ROYAL COMMISSION ON MATTERS OF HEALTH AND SAFETY

ARISING FROM THE USE OF ASBESTOS IN ONTARIO

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Volume XXVI

ROYAL COMMISSION ON MATTERS OF HEALTH AND SAFETY

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VOLUME XXVI

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THE FURTHER PROCEEDINGS OF THIS INQUIRY RESUMED PURSUANT TO ADJOURNMENT

APPEARANCES AS HERETOFORE NOTED

DR. DUPRE: Good afternoon, ladies and gentlemen.

Counsel are there any announcements before we greet the witness?

MR. LASKIN: Let me see if I can get the schedule of witnesses straight for the rest of the month, Mr. Chairman.

As you know, after today, tomorrow we have Mr. Hardy and Mr. Sampson's clients, and I gather the only contingency as to whether they will appear or not depends upon how many flights are being cancelled in the United States and how many are not, but assuming they get here, then we will be sitting tomorrow.

I haven't asked Mr. Hardy, but I wonder if it's possible that we can start at 9:00 o'clock or 9:30?

MR. HARDY: Mr. Sampson is in charge.

MR. SAMPSON: Sure.

MR. LASKIN: Is it 9:00 or 9:30?

DR. DUPRE: Shall we say 9:00 o'clock?

MR. LASKIN: Nine o'clock?

MR. SAMPSON: Okay.

MR. LASKIN: Okay, then as for next week, Mr. Casgrain advises me, at least for now, he is calling only one witness, and that is Mr. Dunnigan, on Thursday, August 20th, and if it's convenient to the Commissioners, I would also suggest we start that hearing at 9:00 o'clock.

Now, as you recall, Dr. Finkelstein's cross-examination has not been completed. Assuming he is available on Thursday, August 20th, I think we can complete Mr. Dunnigan and also Dr. Finkelstein on that day.

Then Dr. Gibbs has agreed to testify on August 21st, and again I would suggest, and I haven't confirmed this with Dr. Gibbs, but if everyone is agreeable, I would suggest we start that at 9:00 o'clock.

Dr. Mustard is shaking his head. No?

DR. MUSTARD: I will not be present before 10:30.

MR. LASKIN: All right.

DR. DUPRE: It will be 10:30 on the 21st.

MR. LASKIN: All right.

DR. DUPRE: Should assume, counsel, that in the meantime we should continue to hold August 19th in case Dr. Dement is available?

MR. LASKIN: Yes. I was just going to mention Dr. Dement. He would like to come. He needs some clearance from his new employer. I won't know the answer as to if he can come and when he can come probably until the beginning of next week, but I will let everyone know.

There are...

M. CASGRAIN: The Thursday is still a hold, is it?

MR. HARDY: Wednesday.

M. CASGRAIN: I'm sorry. The Wednesday is still hold, is it?

DR. DUPRE: That is my understanding.

MR. LASKIN: Yes. Everything is still a hold in the last week. The Monday and Wednesday, the 24th and 26th, are holds in the afternoon only.

DR. DUPRE: All right.

DR. UFFEN: What about Tuesday, the 25th, as a hold?

MR. LASKIN: All day.

DR. DUPRE: Is a hold, and so is the 27th.

MR. LASKIN: Dr. McDonald is still coming on the 27th, Alison McDonald that is.

DR. DUPRE: Does that establish our holding pattern then, counsel?

MR. LASKIN: It does, indeed.

DR. DUPRE: Do the parties have any further comments or questions?

Very well, I understand that today we greet Dr. Kenneth Crump, is that correct?

MR. HARDY: Dr. Kenny Crump, officially, on the birth certificate, I believe.

DR. DUPRE: Dr. Kenny Crump.

THE WITNESS: Right.

DR. DUPRE: I understand that you will be leading the examination, Mr. Hardy?

MR. HARDY: That's right, Mr. Chairman.

DR. DUPRE: Well, may I on behalf of all of us, welcome you, Dr. Crump, most warmly for agreeing to come and give sworn testimony as an expert witness.

Miss Kahn, would you swear in the witness, please?

DR. KENNY SHARMAN CRUMP, SWORN

EXAMINATION-IN-CHIEF BY MR. HARDY

Q. Dr. Crump, I think it might be helpful for the

Q. (cont'd.) Commission if we first have you describe some of your background and how you got involved in the field of risk assessment and biostatistics. Why don't we start with your educational background?

A. Okay. I have a bachelor's degree in electrical engineering from Louisanna Tech University, and a master's degree in mathematics from the University of Denver, a Ph.D. in mathematics with an emphasis in statistics from Montana State University, and the last year of graduate school I spent at the State University of New York at Buffalo in their statistics department.

Q. I gather after you got your Ph.D. you went into academia?

A. I spent thirteen years as a professor of mathematics at Louisanna Tech, that's right.

Q. In the last year you haven't been a professor, I gather?

A. While I was a professor, I was on leave on a number of occasions working in fields related to human health and eventually in risk assessment. I spent a summer at Oak Ridge, I spent part of the summer at the National Heart and Lung Institute, part of a summer at the National Institute of Environmental Health Sciences, and then later I spent almost a year at the National Institute of Environment Health Sciences. That was in 1974 and 1975, and at that time I became particularly interested in assessing of risk from environmental contaminants and took up research in that field, working in the field since that time.

A little over a year ago I resigned from the university to devote my time totally to research and consulting in the field, and I formed my own consulting company.

Q. Starting with the year when you were a fellow at the National Institute of Environmental Health Sciences, did you begin working on publishing some papers dealing with theories

Q. (cont'd.) of risk assessment?

A. I've published about, I guess half a dozen, six to ten papers in the field of risk assessment, in the literature. One of the early papers dealt with some theoretical study of what the shape of carcinogenesis dose-response curves might be at low dose. Later work dealt with procedures, statistical procedures for estimating low-dose risk from high-dose data. I had a contract from the National Institute of Environmental Health Sciences, while at the university, to work on that particular problem.

As an outgrowth of that project, some of the techniques which we developed have been adopted for use by the EPA in the United States, for setting model criteria for carcinogens.

Q. You've discussed a number of projects you've done consulting for U.S. government health-related agencies. Have you also done some consulting for nongovernmental bodies?

A. I've consulted with Kirknell and Ellis on asbestos for the last year and a half. I've consulted with Battelle Laboratories, Electric Power Research Institute, American Petroleum Institute, some other law firms and some other government agencies as well.

Q. What I would like to do today, Dr. Crump, is to talk to you first about some general concepts of your view of how best to do risk assessment, some relationship as we go through them to the asbestos data, and then perhaps go through some preliminary calculations you have done from some of the existing data - risks predicted by those studies.

Perhaps to start we should talk a little about different means of expressing health risks, and maybe you could tell us something about how they are traditionally expressed and your personal preferences on how to express health risks.

A. A traditional measure of risk in an epidemiological study is standard mortality ratio, SMR, or equivalently a relative risk, which is basically a weighted average of relative risks in the various age categories in the cohort, and relative risks which are bigger than one indicate there is some relationship between exposure and a health effect.

That particular measure, although useful for determining whether or not there is an effect, is not particularly useful, in my judgement, for determining the health consequences of an effect.

For one thing, we are talking about a relative risk, and if you have a large relative risk - in other words, you have a much higher incidence of disease in an exposed cohort - if the overall base level of risk, of disease incidence, in the unexposed cohort is low, the amount of..the total amount of disease that you are talking about may still be fairly small.

So, for example, a risk ratio of one point five with respect to something like simple heart disease might be more important as far as human health than a risk ratio of ten for a relatively rare disease.

There are some other measures which can be used for estimating health effects. One of these is the additional risk, additional lifetime risk of a particular disease. For example, if you know the lifetime risk, say of lung cancer, in a standard population, and using some data on exposure to asbestos you could estimate the lifetime risk at a certain exposure pattern of lung cancer in a population exposed to asbestos and just taking the difference of those two estimates, you could estimate the extra risk of lung cancer.

This measure has some advantages over relative risk. I think it also has some drawbacks. For one thing, it doesn't incorporate the amount by which a life is shortened by

A. (cont'd.) death from disease, and I think that's an important issue. Most people, I would guess, are more concerned about when they die more than the specific cause of death, and most people would prefer death to a number of causes at age seventy as opposed to death from any cause at adolescence.

I think the time at which a person dies is an important concept which needs to be taken into account in a risk assessment. One way to do that is to use a measure that incorporates length of life, such as loss-of-life expectancy. This measure incorporates both the risk of acquiring the disease, plus the loss of life resulting from the disease.

I think another advantage it has is that you can apply this one single measure to diseases, to exposures which might cause increases in a number of different diseases. You can compute loss of life expectancy from all diseases combined, and as an overall measure, a single measure, of human risk from a particular exposure.

I think I would...given that you have the data available for making an estimate of loss of life expectancy, I would prefer, I think, using that measure over the other measures I talked about.

I have heard some objections to the use of loss of life expectancy on the grounds that if you estimate a loss of life expectancy of say one month, what that really means is that there are a lot of people that didn't get the disease, but there may be a few that lost twenty years of life, so it doesn't really reflect those twenty years.

However, I feel that any reasonable measure of risk has to reflect both the chance of getting the disease and the resulting loss of life expectancy, and this measure does that.

It's not reasonable just to look at the loss of life in affected persons. If that were the case, we would be concerned

A. (cont'd.) by any risk to children, such as riding in cars, because the ones that do lose their lives lose a great, a major portion of them.

There are some other objections to the use of loss of life expectancy which would also apply to these others in the same way. One objection might be that it doesn't reflect the quality of life. A person may become sick with some disease and live a very low-quality of life for a number of years, but survive.

There are modifications that can take that into account. For example, you might want to look at the loss of life expectancy of a particular quality, and look at the time not until death, but to the time until the diagnosis of a particular debilitating or life-threatening disease, so if one wanted to, you could make that modification to overcome those kinds of objections.

Q. Just to backtrack a little from that means of expressing risk, one other issue I think it would be useful to have you discuss would be the question of whether relative risks stay constant throughout a person's life. I think there has been some discussion of that here previously, and the use of some of the asbestos data, and maybe you could walk us through that issue. It would be helpful.

A. Okay. I've got a slide here, I think, that we can use as the basis for a discussion.

This is a graph of a relative risk of lung cancer in insulation workers, Selikoff's study, plotted against years since onset of work. You see that the relative risk began to rise around a little less, well, at least ten years past exposure on up to a maximum of thirty years past exposure, and from that point on they began to decrease. This pattern is typical. I think it has an important implication for risk assessment.

First of all, obviously if you...if the data is predominantly drawn from this area and you haven't had enough followup and you use that to estimate your relative risk, you

A. (cont'd.) will probably be underestimating the lifetime risk for lung cancer using this data.

But by the same token, if you only use data from this area for estimating risk, you are actually overestimating the lifetime risk.

Ideally, I think, given enough data, what one wants to do is estimate the relative risk, separate relative risk for different age categories and apply those individually to mortality rates to get an overall measure of risk. There is a question as to what sorts of age dependants are most appropriate. If one has enough data, you can estimate the various relative risks individually and that issue is not so important.

If this pattern is generally valid, this suggests that this is the peak at thirty years past exposure and then against five, I would guess that thirty years past initial onset of work is pretty close to retirement age. If one estimates risk from this point out, for example using the retirement population, it doesn't necessarily mean that you are underestimating risk because the average relative risk over here is pretty close to what it is over here.

As a matter of fact, the relative risks at the age categories where most deaths occur are ones that need to be estimated most accurately, and that would be the ones that would occur in the low range.

That's some of the issues in (unintelligible.)

One question, I think, which would be interesting to resolve is to what extent this downward turn is a result of termination of exposure. In fact since there is no data in this particular population as to how long exposure lasts (unintelligible) lung cancer, cigarette smoke, fifteen years past termination of exposure both risks are down close to what they would be for a nonsmoker. The similar sort of thing holds for lung cancer.

Q. In asbestos exposure?

A. In asbestos exposure.

DR. MUSTARD: Excuse me. Can I ask a question?

THE WITNESS: Sure.

DR. MUSTARD: Can you put that back on for a moment? Once you die from lung cancer, you cannot die again. You have taken the cohort through, do you apply a correction on that down curve for the fact that you have lost people who can no longer die - in the estimation of that relative risk?

THE WITNESS: Yes. You do in the sense that here you only look at people which are only ones that are alive at that time. If you apply this to lifetime risk of death, you would factor all that in.

DR. MUSTARD: Let me give you a very simple-minded example from a poor old Commissioner who is not very sophisticated.

You start with a hundred people who were exposed for ten days to asbestos, and you track them through, and they start dying off. Their exposure varied, obviously, they weren't all uniform, and so when you reach the peak, let us say, that you've lost sixty of the hundred, you now have forty people left, those forty people may not have had as much exposure and a variety of other things, and how do you allow for the fact that sixty have died, which have gone out of your hundred, in terms of computing the relative risk of the down slope?

Do you follow what my problem is? You've lost people who no longer can die.

THE WITNESS: Mmm-hmm. Well, what you really want to have, ideally is, have people also broken down as far as their exposure category. Since one does not have that sort of information it could be, like one would expect, that the heavily-exposed person will die earlier than later.

DR. MUSTARD: So that's compounded into that sort of calculation? Thank you.

MR. HARDY: Q. Let me just see if I can help myself understand the issue that Dr. Mustard was talking to you about.

When that curve was constructed, that you just showed in figure one, am I right that the way the relative risks were computed to be put on that chart, for each dot there is an observed number and an expected number, and the observed number is the actual number of persons in the cohort who died of lung cancer between, for one example, thirty and forty years after they started work?

THE WITNESS: A. That's right.

Q. And the expected number is calculated by seeing what the expected number would be for the same number of person years over that period from start of work to thirty-five years later?

A. Well...

Q. And that person-years figure takes into account the number of people still living, in the cohort, during that period. Is that right?

A. That's right.

Q. So that when a person dies, in the cohort, he stops contributing person years to the expected number?

A. Correct. All that is built-in to the analysis.

Q. Moving from risks, which we have been talking about, to health effects, I gather that there is a second significant component to any intent to do risk assessment, beyond health effects, and that's dose or exposure. Maybe you could give us some of your views on exposure, and particularly issues relating to exposure in the asbestos epidemiology.

A. Okay. What one does in trying to estimate risk to some population, one takes a study on the previously-exposed population and just to keep things real simple, just suppose

A. (cont'd.) we have just sort of a linear relationship, just for the sake of discussion, and you have health risks - always put the risk on the vertical axis and dose on the horizontal - but you have some points that might be measures of risk versus dose, and you fit some sort of curve to these data, and you estimate what is the slope of that curve - which I would call the carcinogenic potency, we are talking about a carcinogen - which is really the risk per unit dose. If you only have one point, you divide the risk level by the dose level to compute the potency, which I'll call alpha, and once...this is talking very crudely... once you have the estimate of potency, you would go to some projected future population or a current population, whatever population you wanted to estimate risk to, come up with some measure of dose for that population. So it would be...multiply that times the potency parameter and you would get the risks to this future or hypothetical population you are concerned about.

So the historical data that one uses is to really calculate an estimate of the potency parameter. That involves two quantities - the health risks and the dose - and I would say that they are equally important in computing what that potency is. It's essentially a ratio in the risk that one comes up with. The estimates of potency are no more accurate than the least accurate of those two measures.

I might add that epidemiological studies, including asbestos studies, the health risks are measured far more accurately than the dose measurements. The preponderance of the uncertainty appears to lie in the measures of dose rather than measures of health effects.

Q. What does that mean with respect to epidemiology studies where they just don't have any exposure information on the cohort?

A. Well, I certainly think those studies are

A. (cont'd.) useful. You can compare exposed populations to unexposed populations and get a measure of a relative risk, and determine there was some risk in that population.

One can even study the shape of a dose response by using surrogates for dose, like time of exposure. One good example of such a study might be the study of the amosite factory in Paterson, New Jersey, where you have workers broken down into exposures of less than two months, two months to five months, and so on. Those lengths of exposures are probably pretty good surrogates for the total dose, so one could use a study like that to study what the shape of the dose-response curve might be.

But unless one has an estimate of dose in absolute terms, one cannot estimate potency. I would say that studies in which there are no dose data available are...any estimates that one obtains from those are...there is a lot of speculation involved and they are very uncertain.

Q. One of the particular problems that we've heard a lot about over the summer in terms of asbestos exposurs, is that historically they were measured by particle counting, whereas we are most interested these days in setting standards based on fibers. Have you looked at any of the literature, the information in the literature, on the difficulty of converting particle counts to fiber counts?

A. Yes. I think it's unfortunate that a great deal of attention is given to displaying the health-effect data and interpreting it, and very little attention has been given in the literature to doing the same sort of detail with dose data. With calculating the potency which one needs, they are of equal importance and it is desirable to have more attention given to that issue.

I have looked particularly at the problem with respect to the data in the Quebec miners and millers cohort. Very

A. (cnt'd.) little on these exposure measurements have appeared in the open literature. There's a 1974 paper by Gibbs and LaChance that is based on only about eighty-something measurements.

For the Beaudry Report, there was a study done by Dagbert, who got some data from Gibbs, about six hundred side-by-side impinger and fiber count measurements, and analyzed these data. These are only a subset of the data which are available to Gibbs for estimating these conversion factors that were used in the McDonald study. So I'm not sure exactly how much data in total are available, and I'm not exactly sure of how the data were used.

But I think the data which are available in the Dagbert study I think give us some good indications of the reliableness with which one can estimate fiber counts from historical impinger measurements.

The study was done in French, and I don't read French very well, so I had an associate translate it for me. I have some slides that I took from that study, that I'll show you.

This study was based on about six hundred and thirty side-by-side fiber counts and dust particle measurements made in the Canadian mines and mills. This table just simply shows the average concentrations of...

Q. Dr. Crump, let me just interrupt for a second. I'm afraid this is one transparency that we didn't have a hard copy of.

A. Oh, it isn't?

Q. You can go ahead and use it, but we'll try and get one later of it. Actually, I think of the three that Dr. Crump is going to use, we only had a hard copy of one, which is in the addenda. But we'll get the other two reproduced.

A. This is...if I can direct you to the correct place...as I say, this is taken over about nine different mines and mills, and about eight different types of operations, and they

A. (cont'd.) had measurements in all of these different categories. This just summarized the data we have here, an overall mean of the particle counts - twenty-seven, fiber counts, they use eight one two one. The median of the particle counts is about seven one (inaudible-three or four words).

The important thing is what is the correlation between the measurements of fiber counts and particle counts, and taken as a whole, the correlation, all of these six hundred hundred and thirty side-by-side measurements, is greater than half, which is not a highly-significant result. This indicates to me that there is a significant amount of information in the fiber concentrations based on particle counts, information which is valuable and certainly should be used.

The next transparency - I don't think you have this one either - has the different correlations broken down by different mining areas. You see that they range from a high of twenty-nine three...different mines..to a low of point three four. All of these are significantly positive, indicating a positive correlation between fiber counts and dust measurements.

Q. Could you perhaps give us, we are not statisticians, some handle on how to interpret correlations, whether negative or positive point three, positive point nine?

A. Well, positive correlations indicate that positive values of fiber counts are related to, higher values of fiber counts are related to higher values of particle counts in a linear relationship. The larger the correlation value is, the better the relationship.

Q. If the value were one, that would mean perfect correlation?

A. That would mean perfect linear correlation between fiber counts and particle counts. The relationship of point five...just to do a very crude interpretation of this - I

A. (cont'd.) always perhaps liken it to putting it, one would use that kind of correlation in making estimates - I would liken this to whether you were playing poker, would you, if your opponent offered to show you what he had in his hand, would you take a look at it. I think it's very significant information, that data.

I think the correlation may be even better than the data show. This next slide shows the data broken down not by mines, but by site, mining site, mining operation. So each of the eight observations, each of the eight categories - we are working with categories - is based on observations from eight different mines.

I have ranked them in order of correlations going from high to low - so the correlation for rock screening is the highest correlation, the guy who is doing the mix, then storage, which actually had a negative correlation which indicates there is not very much correlation at all for the storage measures between fiber count and particle measurements.

But I think it's important to notice that at the same time if you look at this column, the average particle counts in these different areas, you see an almost monotone relationship there - very nearly a monotone relationship. So in other words, as you decrease the particle counts this correlation likewise decreases, which suggests to me that at low particle concentrations the particle measurements are highly uncertain.

But on the other hand, for the purposes of estimating old exposures, these side-by-side measurements - these side-by-side measurements were made relatively recently after average concentrations decreased - for the purpose of estimating old fiber concentrations, the data which are most pertinent to this are the data where the dust counts and the particle counts were higher. So these are the data which would probably be most valuable

A. (cont'd.) in estimating those old exposures.

Those are also the ones where one gets correlations in the neighborhood of point seven five, point seven six.

DR. DUPRE: Dr. Uffen?

MR. HARDY: Go ahead.

DR. UFFEN: Could you enjoy a little levity, just for a minute? We've all been away on holidays.

I would like to know how you can show me half a poker hand. You've either got to show me less than half or above the half, not just the half.

THE WITNESS: Six cards...

DR. UFFEN: You've shown me the half of the other cards and I've got more than half of the information.

THE WITNESS: True.

MR. HARDY: Q. We have had some discussion here not only about conversions with respect to the exposure and the data, and the particle counts, in the Canadian mine studies, but also about conversions between particles and fibers at the British textile plant at Rochdale. I wondered if you had taken a look at what is publicly available on those conversions?

THE WITNESS: A. There is not nearly as much publicly available in those data as there are on the Canadian mines and mills. The only data which I have seen was in Peto, et al, 1977 paper in which they give average...a yearly average fiber count versus a yearly average particle count. Although there is some scatter, you see crudely, I believe, a linear relationship between average particle counts and average fiber counts.

Q. Maybe just for the purposes of the record, the table that Dr. Crump is referring to, and which I note has been referred to previously by Mr. Peto, is table five on page 172 of the study which is included in the Peto brief, 1977 British Journal of Industrial Medicine. It's the mortality study of the Rochdale

Q. (cont'd.) plant.

A. It's hard to evaluate that table because you don't know the number of measurements and things like that. You don't really have individual correlations of these averages. These are yearly averages. If you take averages, you can...a lot of individual variation may not be visible when the data are presented in that way.

There is really nothing here which I am presenting that's comparable to that, but I would venture a guess that if these data contained averages in the same way that those data are, you would see probably at least as good a relationship for these data as you would for those data.

There is a table, a chart, in 1974 Gibbs and LaChance that I think shows a great deal of scatter, but you need to keep into account those were on individual measurements, and what we are really interested in are long-term averages.

That's what Peto is actually reporting..(few words inaudible).

I might add that I really don't know exactly how these data and what other data are available - and I'm sure, I know there are other data available - I'm not sure exactly how these data were actually used in computing the conversion counts, but just on the basis of the data that Dagbert presented in his analysis I do believe there is a great deal of useful information regarding proper conversion factors.

Q. We have been talking about problems with historical exposure data and sort of looking forward rather than backward. I would like to have you talk about what you found in trying to determine what future exposures would be, given a fixed occupational standard, which I gather might be relevant to risk assessment.

A. Yes. If one sets a standard, say at two fibers

A. (cont'd.) per milliliter, and one wants to know how effective that standard is in protecting health, the question to ask is probably not 'what is the risk at two fibers per milliliter', but the question to ask is, what is the risk at the average exposures which result from enforcement of the two fiber per milliliter standard, and those exposures will probably be somewhat less than two fibers per milliliter.

The best evidence which I know anything about that relates to this question is that which is in the Simpson Report, which I have a slide of to show you - it's also in the Simpson Report. I was in England this summer visiting various people about asbestos and trying to get answers to some questions, and I visited the person that had these original tables made. He showed them to me and discussed what was available on them.

The factory inspectorate made lots of measurements, fiber counts of various industries. This slide shows the results of that. Five industries - this column here you see the numbers of measurements they made. All these measurements were made after the two fiber per milliliter standard came into effect, and there were a number of measurements. They give us some indication of what the average exposures might be under a two fiber per milliliter standard.

You see the average exposures..sorry, the median exposures...range from one-twentieth...point one would be one-twentieth...of the standard, up for, for insulation board, being one-fourth to one-fifth.

The person I talked to in the factory inspectorate, the health and safety executive, explained that they have a policy in Britain that it is not sufficient to be below the standard, but you are supposed to use available technology to keep things as clean as possible. So this particular value for asbestos ceiling is probably not driven by the standard itself, it's driven by the

A. (cont'd.) policy of having the best practice.

If you are looking at the textile manufacturing as a relatively dirty operation compared to asbestos cement, then point four probably does reflect the two fiber per milliliter standard and indicates, at least in this particular industry, that an average..median levels are a factor of five below the standard.

It would be this level that I would think would be relevant in assessing the effect of the two fiber per milliliter standard on health.

(REPORTER'S NOTE: At this point the reporter indicated a problem recording the witness properly. Steps were taken to rectify the situation.)

MR. HARDY: Q. One other issue with respect to collection of exposure information, which I gather affects the way you would do risk assessments for asbestos, is the pattern or timing of the exposures. I gather you have a few ideas to share with us on that issue?

THE WITNESS: A. Let me say first that the effect of different time patterns of exposure is not understood very well at all, the effect upon health effects. There are some theoretical arguments which could suggest that early exposures are more dangerous than late exposures, and I think that would certainly be true for exposures very late in life where the latency might exceed the expected remaining lifespan.

The data are simply not available for really evaluating which of these models of carcinogenesis might be more appropriate for various asbestos-related diseases. The effects of different assumptions about dose I thought was illustrated very nicely by Berry in one of his papers, Berry and Lewinsohn.

I would like to show you the slide taken from Berry and Lewinsohn, 1979, and they were just investigating one

A. (cont'd.) aspect of the problem, which is how should dose be accumulated. Most of the studies which have dose data which are used to relate to health effects simply use cumulative exposure, maybe up to a certain time or a certain age before death, without regard to whether it is accumulated very early in life or uniformly throughout life.

Berry and Lewinsohn made a theoretical investigation of the effect of different assumptions about how one should accumulate dose on measures of risk. Their investigation was evolved as the prevalence of asbestosis, but the basis argument would apply to mortality of lung cancer or asbestosis or any other asbestos-related disease.

There is one school of thought which suggests that the residence time in the lung might be important, rather than just the cumulative dose - which of course means, as I have mentioned earlier, that early exposures would be more important than late exposures.

So to investigate that, they developed a model in which they had a parameter which gave you how quickly fibers are washed out of the lung. There was not enough data to be able to estimate that parameter, so they simply chose different values to that parameter and looked at what effect different values had on the eventual prevalence of the disease.

One boundary point was the value of instant washout, which simply means you are using cumulative dose, and the other extreme was no elimination at all of the fibers, which simply is equivalent to using as a measure of dose a concentration at a particular time, times the residence time in the lung.

You see that depending on which assumptions you make, you get a difference of eventual prevalence ranging from seven percent to greater than thirty percent. You get a tremendous range in eventual risk, and all of these various models

A. (cont'd.) are equally consistent with the data.

Now, there is one point which I think is very important here. If you look at the eventual...they were using asbestosis data, prevalence data, to fit the models to...if you look at the fit of the models up to twenty years since beginning of exposure, they agree very closely. The reason for that is, most of the data upon which these estimates were based, the typical exposure was twenty years exposure.

So within that range they agree very closely. They only diverge once you move beyond that range.

That suggests something to me about how to deal with various exposure patterns when doing a risk assessment.

These kinds of differences that you see here will not occur if the dose pattern in your cohort is the same as the dose pattern in the population for which you are estimating risk.

In other words, if you are trying to estimate the risk from age twenty through age sixty-five or death with a lifetime occupational exposure, if your cohort you are estimating risk from has by and large that same exposure pattern, it doesn't matter how you accumulate dose as long as you do it the same way in both groups. You will get the same answer no matter how dose is accumulated. So these kinds of large differences will not occur.

So this says to me that one should try to match the exposure pattern in your study population as closely as possible to the exposure pattern in the population for which you want to estimate risk.

Since we can't do controlled experiments in humans, we can't achieve the ideal, but I think there are some things that you can do that will help reduce uncertainty. Some studies, I think, which have very short exposures are inappropriate for estimating risks from long-term exposures. If you have a large cohort such

A. (cont'd.) as the cohort of Quebec miners, you can do some things to maybe help reduce uncertainty.

One might look at a subcohort in which people that begin employment...say you are trying to estimate risks from age twenty through, a risk from lifetime occupational exposure at a constant level, say from age twenty to age sixty-five, persons that entered the study after age thirty - you might not want to consider those at all. Persons who enter around age twenty, but say around age thirty-five leave employment, at some point one might want to consider those lost to view because their exposure pattern is no longer very similar to that for which you are trying to estimate risks.

One could try those kinds of things and one could also, once one has done that, use different ways of accumulating dose, such as Berry has done here, and if the different ways of accumulating dose make very little difference in your resulting risk estimates then you have some confidence that the exposure pattern is no longer a problem in your estimates.

DR. UFFEN: That's only true if it's an exponential elimination, is it?

THE WITNESS: About it not mattering?

DR. UFFEN: When you said that if you had a cohort which has a similar history of exposure, granted at a lower level. That Berry's model assumed an exponential elimination.

THE WITNESS: Yes.

DR. UFFEN: I can see immediately that exponential for both would produce the same results, but I don't see immediately for something other than exponential.

THE WITNESS: Well, uh...

DR. UFFEN: Would it?

THE WITNESS: What I was referring to was this sort of idea, this is what I was referring to: Supppose you have

A. (cont'd.) some type of exposure pattern...it could be a constant exposure or it could be some variable exposure... it doesn't matter what the exposure is. The only difference in the exposure and your study cohort in your target population is just the level. In other words, suppose you have a level here in your study cohort, level down here in your target population, it doesn't matter because no matter how you accumulate dose, the difference in the dose measure you get, the ratio, is simply going to be the ratio of these two values here.

DR. UFFEN: Would it matter what the elimination process is? Say that for the low dose cohort the elimination process could be different than the elimination process for the highly-exposed group. In other words, it depends upon the laws governing the elimination? Does it?

THE WITNESS: Okay, so you are saying that perhaps if you get it as a few fibers retained in the body longer, than if you get a lot of fibers on average?

DR. UFFEN: It may be.

THE WITNESS: Yes. If that is true, then what I am saying does not address that issue.

DR. UFFEN: If you assume the exponential elimination, it holds for both because of the shape of the exponential decay?

THE WITNESS: Yes.

DR. UFFEN: The reason I raised this was, when Mr. Berry was here we talked a little bit about the elimination process, and my recollection was that...I didn't understand how the mathematical construct had any relationship to what actually goes on biologically.

THE WITNESS: Well, I see the point you are making. I still feel like you have far more confidence if you have similar exposure patterns than if you have totally different exposure patterns. You can't deal with all the issues in one view

THE WITNESS: (cont'd.) and I just wonder if this doesn't deal with this problem. But I will still feel more confident with a similar type of exposure.

MR. HARDY: Q. We've talked about estimating doses and patterns of doses. The next issue is determining the relationship between health effects at high doses, which is the area where we have historical information, to health effects at low doses, and that's an area that we have discussed a lot in these hearings and it's an area that you have also written about in some of your articles, including, I think, one that was given to all the participants here.

Perhaps I could have you talk about the shape of the dose-response curve, both theoretically and empirically in terms of the asbestos data.

THE WITNESS: A. Fine. This is certainly a very important issue, and it's one of the main sources of uncertainty in this whole business of risk assessment, because we always had to do is try to estimate what would result from low exposures based on effects seen at higher doses. The sort of dose-response function one assumes is a very critical assumption, and if one believes that a threshold exists and assumes a threshold model, then there would be some dose that's perfectly safe.

The range of different plausible models seems to range from the low end, a threshold, and on the upper end, a linear. That's a pretty big range and I want to say that to eliminate the very extreme cases in which the dose response rises up tangentially with...vertically, initially...and then bends over.

When I say linear, I'm talking about very low doses. I would in linear something that starts out linear and then maybe bends around later on.

There is a very simple general argument that suggests...

Q. Which I gather has had your name attached to

Q. (cont'd.) it, given the article you wrote?

A. Yes. It's a very simple argument which suggests that whenever you have...no matter what the disease is...if you have a fairly significant amount of background incidence without any exposure, at low doses the effect of the exposure might be expected to be linear.

In the argument, it goes something like this: Just take a particular form of cancer which has a spontaneous incidence without any exposure. The cancers that one sees that are caused by exposure cannot be differentiated from those which arise spontaneously. We might infer that they arise from similar mechanisms. It's just that exposure speeds up the rate at which those mechanisms occur.

So if we look at the dose-response curve, we might use a single response curve to represent all of the disease, and assume some effective background dose which is responsible for the background carcinogenesis. So this is risk again, this is dose, so this might be some effective background dose which produces the background tumors. It might in fact be an actual dose of some other environmental pollutants that contribute to that.

Well, one is already out on the dose-response curve past a threshold that might exist, so a little increment of added exposure is just going to elicit an approximate linear response. I'm simply saying nothing more or less than a tangent line you expect to...the slope of the tangent line you would expect to be policy, but once you get out beyond a threshold to a spot where you are seeing some effects. This argument wouldn't apply particularly to carcinogenesis. It would apply to any disease in which you see an appreciable amount of background in the absence of exposure.

Q. Does this theoretical argument apply to asbestos exposures and each or any of the various diseases which have been

Q. (cont'd.) associated with asbestos?

A. I think it would apply...be more applicable to ones in which you have background levels of disease. I think it would be most applicable, probably, to lung cancer in smokers. It would be less applicable to lung cancer in nonsmokers. I think it would be totally inapplicable to a progressive disease like asbestosis, which the severity of the disease is related to the severity of the exposure.

Not to say that one would not necessarily have a linear dose-response curve with those diseases. Just to say that this argument would not support a linear dose response.

Most of the dose-response data I've seen in the various studies for asbestos-related diseases by and large are well described by a very simple linear model. I've seen very little data that would go against a linear model.

I think some of the...there should be, some of the better exposure data are those that come from the study of the amosite factory, that I've graphed here. They didn't actually... they were using duration of exposure as a surrogate for exposure, and it's probably a reasonable thing to do.

For lung cancer, you see some apparently abnormally-high values at very low doses, and then you see pretty much of a linear relationship from that point on.

As a matter of fact, if you do a fit to these data, total data are fairly well fit by a roughly linear sort of dose response. These are not so abnormally large they could be described by a linear relationship, and I remind you that I'm plotting extra risk of death so there is a sizeable background of carcinogenesis at zero dose here, which is not graphed on this slide.

Q. That's because we are talking about lung cancer in a cohort that probably included a large number of smokers?

A. Yes. I would say probably most of these cancers are in smokers and we are really looking at the shape of the dose-response curve in smokers, primarily. That would be my guess.

DR. DUPRE: Dr. Crump, what is the cohort that is being referenced here? It's an amosite factory?

THE WITNESS: It is the amosite factory.

DR. DUPRE: Which...?

THE WITNESS: In Paterson, New Jersey.

DR. DUPRE: Oh, this is the Paterson cohort?

THE WITNESS: Yes.

MR. HARDY: The Seidman study.

THE WITNESS: The Seidman study.

MR. HARDY: Q. And as I understand it, just to make sure we understand this chart, you are using time of work in the plant as a surrogate for exposure, because we don't actually have exposure estimates?

THE WITNESS: A. Yes. Yes, this study, I think, is good for studying the shape of the dose-response curve, but unfortunately it's not so good for estimating potency because we don't know what the actual exposures were. We don't have any measurements of them.

The mesothelioma data are...

Q. Why don't we just do one other thing for the record, which is - that's one of the few charts in the addenda that we don't have a number for. Why don't we make that one figure four.

A. Four?

Q. Figure four, because we have three other figures previously numbered in the set.

A. The mesothelioma data are consistent with a threshold up to something below six months exposure, and they are also consistent with...I haven't actually figured this out

A. (cont'd.) analytically, but I'm sure they are also consistent with a linear relationship between risk and dose. Something like that.

The asbestosis data are...and this is based upon death certificates, not upon what they call best evidence...the asbestosis data, you don't see any response at all until you get out to the greater than two years, so that's certainly consistent with a threshold. But again, it's also consistent with a small increase at lower doses, and a curvilinear, a higher increase at higher doses. I am fairly certain that it is inconsistent with the exact linear relationship.

I would think that this should be some of the better data for evaluating shape of the dose-response curve, even though I admit it's not a very high quality because of the difficulties in measuring the dose. There are quite a few studies that actually have individual dose measurements, and those measurements are quite uncertain.

In animal experiments, it's very easy to be very accurate about dose. Well, let's put it...much easier...you have much less uncertainty than you have in human studies. Even there the shape of the dose-response curve is very uncertain, and I would say that would apply much more so here because of the uncertainty as to the actual dose level.

Q. I gather, Dr. Crump...you have talked about this data and I think you referred to other epidemiologic data on asbestos...fitting for the points for which data exist, a linear relationship. Does that mean necessarily that for lower exposures the relationship is just a continuation of that linear line?

A. No.

Q. In other words, that linear relationship at high-dose levels might also be consistent with a curvilinear relationship, or even possibly a threshold, at lower levels, for

Q. (cont'd.) which there just isn't data in the study?

A. It could. I think the risk does not have to be much greater than what is predicted on a linear relationship. I think there are cases where the risk would be much less than were predicted by a linear relationship.

Given the uncertainty in the dose measurement, even if the relationship is not linear I wouldn't be surprised that a linear model would pretty well describe most of these data, because of the misclassification of dose.

If you were to look...suppose we had a study in which the true response was threshold...say this is lung cancer so you would have some background...and most of these studies have only about three or four dose levels...suppose there is absolutely no increase until one gets out here at the highest dose, so the true response is the threshold. Because of the uncertainty in the measure of dose, a linear relationship might very adequately describe these data. If some of these people in this classification should have been over here, and vice versa, it would make no difference because they have a flat level anyway.

But some of these should have been..were inadvertently classified over here, then it would tend to lower the actual observeds value, and if some of these were inadvertently classified over here, it would tend to raise this value and tend to make the curve appear linear even though it really rose from a threshold-type situation.

So I guess my feeling is that the dose-response data that we have available is really very uncertain and really inadequate in really determining the shape of the dose-response curve.

Q. I gather further that if we did assume a linear dose-response curve for any of this data, what we would be doing is

Q. (cont'd.) conservatively estimating risk? In other words, estimating the highest likely number for the risk?

A. My opinion is, a linear relationship is not apt to underestimate risks appreciably. It may be about right in some cases. It may overestimate risk considerably in some cases.

Q. Putting together all of the various issues we have talked about up to this point, do you have some sort of criteria that you would apply to judge whether any given epidemiology study is best suited for risk assessment?

A. Here's some criteria that I've applied that relate particularly to risk assessment, but some other issues about the general validity of an epidemiological study, which I haven't included here, but these are some which I think are particularly pertinent to risk assessment.

First of all, I have rated these roughly in order of importance which I think I would place upon them. I feel in reviewing the literature there is evidence that is some differential risks from different types of fibers, and even from different processes that use the same fiber type, and whether this is due to different physical dimensions of fibers or chemical dimensions, for whatever reason, in the epidemiological studies there does appear to be a differential in risk from various materials. So I would put the identity of the asbestos material rated quite highly.

If you are trying to estimate risks from exposure in a textile mill to chrysotile, I would endeavor to find a study that had exposures to that material in that setting, to estimate the risks. Even if the study were not so appropriate in other respects, because I think that's a very important issue.

Of equal importance I would...is the quality of the exposure data. I think that element is of equal importance as the health effects data, and to try to use a study for which

A. (cont'd.) there are no historical exposure measurements to estimate risk, is in my judgement only slightly more appropriate than using current data in factories for which we can measure the data, measure the exposures, but we can only guess what the future risk might be.

Both of those situations, you lack the key ingredient in risk assessment. So I would rate low the studies in which exposure data is nonexistent or of sort of hearsay evidence.

Because of the strong interaction between smoking and lung cancer, I would want to have some smoking data available on the cohort, preferably individual evidence, collected at the individual level and not just overall rates of smoking.

Also, I think, as I mentioned earlier, I would like to have an exposure pattern in the cohort which is roughly comparable to the exposure pattern in the target group for which I want to estimate risk. I might make some adjustments to the data to enhance that area.

The age distribution...you wouldn't want a preponderance of young ages and also we want...if I'm faced with the use of a small study or a large study, I'm going to have a large study so you have less statistical variability.

If you do have a larger study then you can make some adjustments to the data to compensate for items four and five.

So those are, I think, in addition to basic epidemiological factors that are considered in any study, these are some which I would consider and relate particularly to risk assessment.

Q. Perhaps, leaving those criteria on the screen, you could give us some of your views on the appropriateness of some of the studies we have heard so much about this summer, on asbestos, for risk assessment purposes.

A. First of all, I think the McDonald study of the asbestos mines and mills in Quebec satisfied these criteria better than any other. However, because of the possible differences of fiber types, I wouldn't necessarily use that study to estimate risks in every setting. And if I did apply it to another setting, I would certainly want to make some adjustments for the possible different carcinogenicities or potencies of the different types of fibers.

But it's a very large study, the exposure is almost entirely to crocidolite...I'm sorry, to chrysotile. They have very detailed exposure data on individual exposure measurements, they have smoking information available. It's a large study in which they have a variety of exposures. They have a significant number of very long-term exposures, which I think are particular appropriate for estimating risk from long-term exposures.

In those criteria, I would rate the McDonald study as the very best.

DR. DUPRE: Including criterion number two?

THE WITNESS: Yes.

DR. DUPRE: Tell me, exactly what do you mean by criterion number four - exposure pattern of cohort?

THE WITNESS: Short-term, intermittent exposures versus long, continuous exposures. What I'm thinking about is, we want to estimate exposures, say from lifetime occupational exposures, to some future working population. Since we don't know, it's hard to determine what the relative effects of different exposure patterns might be. I think the uncertainty is reduced if you have a population which has experienced long-term lifetime exposures as well.

DR. DUPRE: If I...well, no, I'm not going to try to understand. I'll simply ask you the question that's on my mind. Where does the McDonald study fit, in your view, with criterion

DR. DUPRE: (cont'd.) number four?

THE WITNESS: I think it rates highly, because it does have some short-term exposures, but it has, you know, enough long-term exposures that one could simply look at that subset and base risk estimates upon that particular group.

DR. MUSTARD: Could I ask another question?

MR. HARDY: Certainly, Dr. Mustard.

DR. MUSTARD: Your application of number six, does that take into account the problem of the kind of exposure that people have in relation to whether there is going to be a large amount of downstream problem occurring? In other words, if I exposed a hundred people in circumstances...and you alluded to this in terms of fiber type, etc....and we are going to have fifty percent of that work force come down with health problems in twenty years, it seems to me that would be a different kind of problem, would it not, than if I exposed ten thousand people in which maybe one percent would come up with problems in twenty years?

In other words, how do you balance off the size of the study in terms of the number of people that are going to manifest a problem?

I could pull a large cohort in, but it might not have had exposure to the very powerful effects in terms of fibers.

THE WITNESS: I see. I would...if I were given a single measure of size...talking about number six?

DR. MUSTARD: The size of the study in relation to exposure...

THE WITNESS: Yes. I wouldn't use the number of people involved in the study. I would use probably the number of deaths as a measure of size.

DR. MUSTARD: Okay, okay.

THE WITNESS: As the most appropriate measure of size.

DR. MUSTARD: So if I had three hundred workers exposed, and a hundred deaths, that would be a strong study, would it?

THE WITNESS: Not as strong as one in which you had five thousand workers and a thousand deaths.

DR. MUSTARD: Right. But if I had three hundred and a hundred deaths, it would be a stronger study than ten thousand workers and, say, fifty deaths?

THE WITNESS: Yes.

DR. MUSTARD: Thank you.

THE WITNESS: That's a crude sort of measure of size, and I don't really rate that very highly. I really think the first two, and possibly the third, are the ones I would give the most attention to.

DR. MUSTARD: But surely there is a seventh one that should be on there, and that's the outcome we are after - deaths. That's an important...surely that has to be important in considering the quality of the study, the quality of the data. But the amount of ill health...

THE WITNESS: The size of the effect.

DR. MUSTARD: Yes.

THE WITNESS: The size of the effect.

I'm not sure that I would...

MR. HARDY: I'm not sure Dr. Crump understands. Perhaps, let me...

MR. HARDY: Q. I think Dr. Mustard is asking about the quality of the health information - do we know for sure the true cause of the death of the persons in the cohort.

THE WITNESS: A. I thought he was asking about the size of the effect...if the relative risks were like an order of ten, would that be more important...

Q. We'll let Dr. Mustard...excuse me.

MR. HARDY: Let me go right out of the question.

DR. DUPRE: Just speak for yourself, Dr. Mustard.

DR. MUSTARD: Thank you.

I'm used to end point analysis in clinical trials in which we have soft end points and hard end points, and I learned in the asbestos thing even with deaths we have a softness in death classification that comes up. So we have two problems - the size of the effect and the quality of the data about the death and the number of people not followed up who may have died and we have to make some kinds of assumptions about.

It seems to me that those are important determinants because the end point, the quality of the end point data in terms of size, the quality of the evidence and the missing people, the information we've had is also an important thing in considering the criteria of the study.

I may be wrong in that, but I would like to...

THE WITNESS: I'll agree with that. I didn't include that, and I did mention that I would categorize that on saying that I was ranking qualities which I think pertain particularly to risk assessment. I certainly think that's important and would be important in any epidemiological study whether you were going to be doing risk assessment with it or not. The degree of followup, and that sort of thing.

MR. HARDY: Q. I think we were talking first of Dr. McDonald's study and how it fits into these criteria. Do you want to apply these criteria to any other studies?

THE WITNESS: A. Well, the study of the U.S. and Canadian insulation workers by Selikoff, et al, is a large study, there's good followup, they went to great lengths to determine the cause of death. There's a particularly appropriate...a control population that was used, they have information on smoking, individual questionnaires or data on individual smoking. I would rate it high in all those respects.

A. (cont'd.) With respect to asbestos material, they were exposed to a mixture of chrysotile and amosite. It can be very difficult to separate out the effects of those different types of exposures. I wouldn't rate it so highly there.

As far as quality of the exposure data, I think this is a very important point. I would rank it low, since exposure data is essentially nonexistent.

So I think that's an essential element, so because of that I would give it overall a low ranking.

I'm not saying I wouldn't use it because of the importance of the identity of asbestos material. It might be most appropriate in some circumstances.

The Seidman study had exposure...now, this is the Paterson, New Jersey factory...had exposure apparently totally to amosite, so for...if you are going to estimate a risk from amosite, I would give it a high mark there.

Smoking information is available. I would give it a high mark. As far as I know there were no environmental measurements made in that factory, and because of that I would give it low overall marks for appropriateness for risk assessment.

If we are going to estimate risks from long-term exposures, I also give it a low mark on number four because the maximum exposure in that factory was four years.

DR. DUPRE: I wonder if I could ask a question, counsel, which is on my mind here. As I listen to Dr. Crump, in what I find is a very, very useful and interesting exposition here, my mind keeps going back to table thirty-five in the Simpson Report.

THE WITNESS: Right.

DR. DUPRE: Which, of course, at page seventy-five gives us the four studies that the Simpson Report used in their essentially quantitative risk assessment. Of course as I look at

DR. DUPRE: (cont'd.) that table and as I listen to Dr. Crump, I see he has pointed out some of the problems with the Selikoff study and the Seidman study. I simply observe that what I am hearing from him, of course, coincides with the Simpson Report...the view that indeed whatever the merits of these studies, they could not be used for the kind of quantitative risk assessment exercise that the Commission was involved in.

Will you have an opportunity or will it be possible for Dr. Crump at one stage to tell his view, as he told us his view on the McDonald thing, to give us his opinion on the two Enterline studies and on the Rochdale study which were used?

MR. HARDY: Certainly. Let's do it right now.

THE WITNESS: The two Enterline studies?

MR. HARDY: Q. Well, the Simpson Report, table thirty-five, as you recall, as you will see, presents different estimates based on the production workers and the maintenance workers.

THE WITNESS: A. Okay. I would give the Enterline study intermediate marks between McDonald's study and the other studies I have mentioned. As I recall, it's intermediate in size, there was exposure to different fiber types, but they did have some information on a considerable group that was exposed exclusively to chrysotile, so it might be possible to ferret out the effects there.

Smoking data was not available for the entire cohort but...on an individual basis. I believe they had a sample of smoking data which showed that they were...smoked about as much as the general population. But I would prefer to have individual smoking questionnaires.

I think these people were by and large long-term workers. Their average exposure was over twenty years. I would give it I think a fairly good mark there. The fact that they are retirees I think detracts somewhat from the study. How that affects the actual risk estimates, I'm not sure.

Q. I think you referred earlier this afternoon to what sorts of results might be expected in studies of retirees.

A. Yes. If that pattern that Selikoff found holds in this study, then there might not be any bias because these are retirees. On average you may still have about the right lifetime risk estimated.

The Rochdale study is not a very large study. Exposure is primarily to chrysotile, so I would, I think, give it, for estimating risks from chrysotile exposure in a textile plant, I would give it high marks for that purpose.

The exposure data has not been completely elucidated. I would have some question about exactly what their exposure data really is. Apparently they have average exposures in the plant by year, estimates, and I think the kind of data in which you have coupled work histories with area-wide measures to come up with individual history of exposures is preferable to that kind of data.

They don't have smoking data, so I would give it a lower mark there, I think. I would like to have smoking data. So I think they both have some strengths and they have some weaknesses.

DR. DUPRE: Dr. Crump, I would like to share with you this observation of someone who has been to the summer school that Mr. Hardy is referring to when he asks you for your very interesting views on this.

As a layman, on the basis of my summer school experience, I would hazard the nonexpert opinion that the Rochdale study would rate somewhat higher in terms of all the exposure data, than the McDonald study. I simply had in mind there the extent to which there seems to be, in terms of the post-1933 data on particle counts, some assistance from the dust level regulatory regime that went into place in Britain in 1931, and which apparently gives them at least an historical time series on exposure data that may have been more helpful to them

DR. DUPRE: (cont'd.) than the data that Dr. McDonald had.

THE WITNESS: I think part of the problem I have with their data is, I don't know a great deal about the exact nature. You know, just generally speaking I would prefer individual exposure measures to just area-wide exposure measures.

I wouldn't necessarily rate the data above that of McDonald, but I'm not sure they are really below either as far as exposure data are concerned.

DR.UFFEN: Could I ask you about this? Isn't - there isn't any nice, orderly way to approach things? However, one would be tempted to put the weight against those six criteria and maybe a seventh, or an eighth, because it becomes a matter of judgement.

What puzzles me is that if I put weight and you put weight, and everybody else puts weight, they are going to be different, probably, because of our knowledge and experience. If I sum the weights, do we all get the same result? Because what I weight highly, you rate lowly, and when we add it all up we all get an index which is pretty near the same?

THE WITNESS: I don't know. I don't think you can make a really hard and fast rule.

DR. UFFEN: It's a nice exercise to try...get a few people like you and ask them to put weight on it, and then sum the weights and see what the dispersion is in the assessment.

See, for me it's nice, it's orderly, but I haven't any way of knowing whether your rough index is the right one or not - you know, increasing the importance at the top? But you tried to weight them.

THE WITNESS: You mean actually assigning a numerical index to those?

DR. UFFEN: Yes. Assigning a weight of ten to

DR. UFFEN: (cont'd.) number one, and nine to number two, and then down, and then apply it to the various studies and see what the index of reliability is for each study?

THE WITNESS: As a matter of fact, I have experimented with that sort of idea and I've decided, I think, as a result of that experimentation that it's not a very good idea. Really, one cannot make hard and fast judgements on these kind of issues, and I view this just as a framework for considering the various issues involved, more so than making a hard and fast decision as to what is best and what's worse, and what should be used and what should not be used.

MR. HARDY: Any other studies you are particularly curious about, Mr. Chairman, in terms of these criteria? We could, I suppose, move on to a different subject.

DR. DUPRE: I have no other suggestions, thank you.

MR. HARDY: Dr. Uffen?

DR. UFFEN: Were going to...in referring to this paper once, were you intending to come back to it at all?

THE WITNESS: No, I wasn't. But if you would like to talk it, now would be a good time.

DR. UFFEN: Mainly a clarification of something...

THE WITNESS: Sure.

DR. UFFEN: Two things in it that I didn't quite grasp, and for purposes of identification it's page two nine seven seven, where you were talking about your analyses of the various models and you made a statement about the applicability of the theoretical models. It's not long. Perhaps if I read it to you?

THE WITNESS: This is the 1976 paper?

DR. UFFEN: The 1976 paper, what we call tab one. "We note again here that this analysis is appropriate only for those agents that affect cancer incidence through alteration of single cells in an irreversible and heritable manner".

DR. UFFEN: (cont'd.) I stumbled over the inclusion of heritable. Does that have to be in there?

THE WITNESS: I think it's referring not to generation inheritance. It's a cell-to-cell type of inheritance, and I don't think it has to be in there, and as a matter of fact... before I say this for sure, can you tell me where you are reading from?

DR. UFFEN: Oh, I'm sorry. Page two nine seven seven, top of the right column...the paragraph that begins, "We note again here".

THE WITNESS: Okay. The basic argument that I roughly outline here, which is also outlined in this paper, I think has wider application than we indicate here.

DR. UFFEN: Were you thinking about radiation-incuded mutations, and so on, when you wrote this thing?

THE WITNESS: Not particularly, but that would include that.

DR. UFFEN: Okay. I have one other...it may be trivial, but I would like to...oh, yes.

On the same article, page two nine eight zero, righthand column down near the bottom where you are talking about practical implications. You talk about probit...

THE WITNESS: Two nine eight zero?

DR. UFFEN: Two nine eight zero...

THE WITNESS: Mine stops at...

DR. UFFEN: Pardon me, two nine seven eight.

You had been talking linear extrapolations and interpolations, and then you introduced probit extrapolations, which is not an expression that I understood. Could you explain a little bit about that?

THE WITNESS: Sure.

DR. UFFEN: And whether or not we need to pay any

DR. UFFEN: (cont'd.) attention to it.

THE WITNESS: Well, in answer to that..I'll not answer the first question. I think the answer to that is no, you don't really need to get into it.

DR. UFFEN: All right.

THE WITNESS: Is that good enough?

DR. UFFEN: Yes.

MR. HARDY: I've always wanted to ask that question, too, but we'll do that some other time.

MR. HARDY: Q. We've been talking a lot about principles of risk assessment, and your judgements on how to best do them, and I think you've done some preliminary calculations based on the McDonald data which take us through the steps you would use in making a risk extrapolation from that data. Maybe if you could take us through what you've done, then give them the charts to do it with, we would see how these principles are used in action.

I think these charts are all going to be in order as we go through, so they should be pretty easy to follow.

THE WITNESS: A. They may not be exactly in order, but they are all...

Q. But they are all numbered.

A. I made some calculations based upon the McDonald data. Quite frankly, a lot of the issues that I've discussed here one cannot apply or take account of the way that I would like to, because this had to be based upon the published data. Some of the data that one needs just was not published.

Q. Would this be data that's unavailable, or just not published?

A. It's just...the raw data is not presented in a way that would be appropriate for what I would like to do with the data.

A. (cont'd.) Because I think it's important to consider the effects of smoking, the interactive effects of smoking and asbestos exposure upon lung cancer, I decided to base the analysis and tell you about this table here, which comes from McDonald et al, 1980, paper, in which he has broken the cohort down by degrees of dust exposure accumulated at age forty-five, and by degrees of smoking. Those are the categories he has the observed numbers of lung cancer deaths and the expected number based upon a reference population.

Dust exposure accumulated at age forty-five may not be the most appropriate measure of dust, but this is the only one in which he breaks out the effects of smoking, at least in a prospective type of study.

So the first thing I did was fit some mathematical models to these data to see how well they fit. I can fit a number of things to these data. I'll just mention two things.

One is what I call a multiplicative model...the RR stands for relative risk...the alpha, beta and gamma?...delta. The alpha, beta delta are parameters if you estimate the data. D is asbestos dose, X is cigarette dose.

In the multiplicative model...we'll call it multiplicative because the effect of smoking multiplies the effect of asbestos exposure, and vice versa. There have been some investigations into the interaction of smoking and asbestos to suggest that the effect is indeed multiplicative.

But each of...the effect of each exposure taken by itself is linear. In a fixed level of smoking, the relative risk varies linearly with respect to asbestos exposure.

The additive model is similar, except the effect of smoking adds to the effect of asbestos exposure rather than multiplying it.

So, I took these two models and actually a number

A. (cont'd.) of other models, and fit them to the data to see what happened.

Here are the results of this exercise.

Q. This is table four, for the record.

A. What I have here are the actual numbers predicted by these two models compared to actual observed values, the numbers of lung cancers, I have the parameter estimates, and I have the results of a chi square electron spin test.

The P value for the multiplicative model is point seven six, which indicates that this model provides a very adequate fit to these data. The P value for the additive model is point zero one, which indicates that the fit of the additive model can be rejected by this point zero one level.

The smoking levels were not given by McDonald at all, so I had to just assume the values for the smoking levels. I just gave them nonsmoking, moderate and heavy smoking.

I did change these numbers up in ways that I thought might be reasonable and didn't materially affect the fits of these models to the data.

So the multiplicative model fits quite well. The additive model didn't fit very well at all.

I actually used some other models in which the relative risk varied as a square of smoking or as a square of asbestos exposure. None of those models materially improved the fit of the multiplicative model in which the variation was linear with smoking and with asbestos exposure.

So I decided to use the results of fitting on the multiplicative model to estimate risks of lung cancer.

Essentially all I get out of this fitting is the value of this potency parameter for asbestos. This alpha is the asbestos potency parameter point zero zero one five nine, so that means essentially that the relative risks from exposure to

A. (cont'd.) asbestos will be one plus alpha is point zero zero one five nine, times the dose. That's the model that I'm using.

It's age independent. It might still happen that these relative risks vary with age as are observed in the Selikoff cohort, but there are no data available in this published data to take that possibility into account, so I am assuming a simple constant relative risk over all ages.

Now, since I want to estimate risks separately in smokers and nonsmokers..let's see, this is table six. I'll show you table five first...I wanted some age-specific mortality rates which could be applied to smokers and nonsmokers separately, and I used two sources for such data. One is the smoking study of U.S. veterans, made a number of years ago, and what I get from the study are the mortality rates in nonsmokers and smokers for all causes and for lung cancer.

Since future populations may have different mortality rates than these U.S. veterans, it's worthwhile to look at other populations in addition to just this one, so I also looked at the smoking data from the British doctors.

Now, the same type of data are available for both sources, the age-specific mortality rates for smokers and nonsmokers taken separately for lung cancer and for all causes.

The estimates that I'm going to come up with are a function of these mortality rates in that potency parameter of alpha which I estimated on the previous slide, and I think I can sort of just generally tell you what I did.

First of all, risk of lung cancer, risk of dying of lung cancer, can be calculated from these lung cancer rates and the total mortality rates. Likewise, a life expectancy can be calculated from total mortality rates. And this gives the mortality rates in nonasbestos-exposed persons, which I'm going to use, and

A. (cont'd.) the only thing that remains to be done is to estimate those rates in asbestos-exposed populations and plug them into the appropriate formulae.

The way I did estimated dose for asbestos exposure is quite simple. Take the one hundred and twenty-six value for lung cancer in the fifty-five to fifty-nine age group - the mortality rate is a hundred and twenty-six with that exposure to asbestos. I estimated the effect of exposure to asbestos by multiplying that value by one plus the alpha, which was estimated in the previous slide, times dose where dose is cumulative exposure to age forty-five.

Once you get those things estimated, you just plug in the appropriate formulae to get extra risk of lung cancer death and loss of life expectancy.

Now, I guess the only remaining question is what dose to plug in there, and I started to ask the question of what risk would result from exposure under a two fiber per milliliter standard. So I had two fibers per milliliter, I wanted to account for the fact that the true exposure might be less than two fibers per milliliter, I decided to divide by two and assume that on average a two fiber per milliliter standard would result in an average exposure of one fiber per milliliter. The data from factory inspectorate of Great Britain indicates this might be a conservative assumption, that true exposures might be less than that.

The measurements which were made, the measurements of fiber counts which were made in the McDonald data, are made by static samplers and the standard might be enforced by personal samplers. There's some indications that there's a difference in the measurements you get from static samplers and personal samplers, and I'm sure the data indicate that effect is quiet variable depending on where you have the static sampler in relation to the

A. (cont'd.) individual.

There is some data in the Simpson Report that indicates that personal samplers give higher readings on average that are greater by a factor of two, so I decided to use that value, so I put another factor of two in there to account for difference in personal versus static sampling.

The most recent paper, McDonald et al, indicates that on average one million particles per cubic foot is equivalent to three point one four fibers per milliliter, so that would be three point one four fibers per milliliter per particles per cubic foot.

So this converts fibers per milliliter to particles, million particles per cubic foot. Now, what we need to plug into the equation is the total exposure through age forty-five. If we assume the exposures we get at age twenty and up to age forty-five, multiply by that, and you get, I think, four point zero million particles per cubic foot years.

Q. So that would be the cumulative dose for a worker working for twenty-five years at a two fiber standard?

A. Yes, that's what that represents.

Q. Put in terms of particle counts?

A. Yes.

Q. In order for you to use the McDonald data to estimate risk?

A. Yes. Cumulative exposure to age forty-five is the appropriate thing to calculate here because that was exposure which was used to estimate the potency.

Okay, so basically what I did was use this for the dose, plug in that linear relative risk model that I showed you, and this next slide shows you the results of that.

MR. HARDY: Table seven.

THE WITNESS: Table seven.

THE WITNESS: (cont'd.) I estimated risks separately in smokers and nonsmokers. You take the best estimate of the potency parameter, the extra risk of lung cancer - no matter whether you use the British doctors or the veterans - is around the order of one in twenty thousand.

MR. HARDY: Q. That's for nonsmokers?

THE WITNESS: A. For nonsmokers.

If you look at the...if you take the upper and lower confidence limits of that potency parameter it varies from about one in fourteen thousand to one in fifty thousand.

There seems to be relatively good agreement between using the British doctor data and the U.S. veteran data.

That is an area of uncertainty because what you would really like to be using are the mortality rates of some future population, which you don't have available.

For smokers, the risks are on average about twelve times higher, it looks like, on average. The extra risk of lung cancer from the asbestos exposure, the best estimate is like one in two thousand. Confidence limits range from one in thirteen hundred to one in forty-nine hundred.

The next slide shows estimated loss of life expectancy - the same situation as I had in the last slide. For nonsmokers, the best estimate is point one six days for... using the British doctor data...and point two using the U.S. veterans data. That's roughly about three hours.

Q. So what you are saying there is that your calculation says that the average loss of life expectancy for twenty-five years of work at the two fiber standard is about three hours for nonsmokers, for lung cancer?

A. That's what this estimate shows.

Q. And for smokers, about two days?

A. Yes. I really think the estimates might be

A. (cont'd.) applied to not just twenty-five years of exposure, but to longer exposure because the actual McDonald cohort was exposed for longer than twenty-five years. It's just that they only accumulated dose up to twenty-five years.

DR. MUSTARD: This is also based on the kind of fiber and kind of exposure that occurred in the Quebec mines?

THE WITNESS: Your estimating..?

DR. MUSTARD: I mean this estimate applies to that?

THE WITNESS: Yes. I would be reluctant to apply this outside that context.

MR. HARDY: Q. It's a little hard to know what it means to have an average loss of life expectancy of three hours or two days. Do you have some means of putting that in context?

THE WITNESS: A. I have a slide here that estimates loss of life expectancy from other types of endeavors. It might help to put that in context.

Q. This is table fifteen.

A. I have here loss of life expectancy from occupational accidents (few words inaudible) change from the paper by (inaudible)...I'll give you the exact reference, if I have it... the Journal of Health Business, I believe, in which he says...

MR. HARDY: Dr. Crump, I think the reporter is having a little bit of trouble.

THE WITNESS: Oh, excuse me. I don't mind him interrupting if he's having trouble.

Okay, for occupational accidents, these estimates, as you can see, range from thirty days to three hundred and twenty-eight days. It's interesting that the highest risk comes from mining and quarrying. I'm not sure if these can be applied to the Quebec miners or not, but if they can, it's obvious that they are comparing this estimate of loss of life expectancy to that on the previous slide. It's obvious that their risk from

A. (cont'd.) asbestos exposure, given that these estimates are correct, would be a very minor portion of their total occupational risk.

Q. I guess what we are comparing is, when you make that statement, is the average loss of life expectancy among miners is three hundred and twenty-eight days because of accidents, versus the risk we have been talking about of three hours for nonsmokers,

A. ...two days.

Q. ...and two days for smokers.

A. Right.

Another risk which might be related to occupation would be commuting to work by automobile, so I estimated a loss of life expectancy using the U.S. 1976 traffic accident statistics and mortality statistics, and using their estimate that roughly thirty percent of all travel in the United States is to and from work.

If you use that estimate, you get a loss of life expectancy for commuting to work by automobile of seventy-eight days.

I also have three estimates of loss of life expectancy from smoking. There is a problem here because mortality rates from a lot of different diseases are increased among smokers, but some of these may be due to confounding with other types of exposures.

For example, smokers have a higher incidence of cirrhosis of the liver than nonsmokers, but this is probably due to confounding with drinking habits rather than due to smoking. So because of the uncertainty there, I provided three estimates. The first category are mortality from diseases which were fairly certain. This dichotomy is actually based upon what Doll and Peto have in their 1976 paper - that's Richard Peto, Julian's brother, by the way.

A. (cont'd.) So you get six hundred and ninety days for those diseases which you are fairly confident are caused by smoking. You add that to category two A, which is likely to be caused by smoking, it doubles it, and there are various other causes which I haven't listed here which are probably, in the words of Doll and Peto, attributable to smoking. If you include those you get sixteen hundred and eighteen days. What's that? Roughly four years?

Q. What sort of smokers do they calculate that for?

A. I think we are talking about the average amount smoked by the smokers in the Doll and Peto study of the British doctors, and their average smoking rates, I believe, is about eighteen cigarettes a day. Not heavy...I wouldn't call that heavy smoking. Average smoking? I don't know. I think heavy smokers smoke more than that.

I think it's instructive to apply, compare this with the risk to smokers that were estimated in the previous slide, which is around two to three days, and if those estimates are valid then we see that the smokers' risk of lung cancer is affected only very slightly by their asbestos exposure in this situation.

Q. I think you talked about the lung cancer risk calculated from the McDonald study, but I believe you've looked at some other possible health effects and accumulated - not only lung cancer effects, but some of the other risks that appear to come out of that data?

Table twelve might be the best.

A. I applied similar procedures to estimate risks of cancer of stomach or esophagus, using some data that was in the McDonald study, and there is no evidence that I know of that relates those diseases to smoking habits. Nevertheless, I made

A. (cont'd.) the risk estimates separately for smokers and nonsmokers because they do have different mortality patterns, and you see that even though in fact the extra risk of death from stomach cancer is greater in nonsmokers, simply due to the fact that they live longer and have longer to contract the disease, it turns out in nonsmokers this procedure estimates the risk of stomach cancer to be greater than that of lung cancer.

But for smokers, the lung cancer risks still dominate.

The pneumoconiosis risk estimates, I feel are even more questionable than the ones I have already presented. I didn't feel like the method I was using was appropriate for disease such as pneumoconiosis, which is not diagnosed unless you have exposure to some type of dust, and what we really would like to have is the extra risk, given exposure versus no exposure to asbestos, and the procedure I have been using was not appropriate because those cases that you see in the general population are not background cases, but they are caused by exposure to some material, whether asbestos or something else. So I use a different approach for pneumoconiosis just in order to be able to generate some numbers.

I looked at the total excess number of cases of pneumoconiosis in the McDonald study, then I looked at the total excess number of cases of stomach cancer, and got that ratio, and I assumed that ratio would hold more widely and actually use that ratio in this situation.

At any rate, down on the bottom line there I have the totals, and everything is linear here so you can get the total risk of all these diseases by adding things up in the columns, and in nonsmokers from all the disease I have considered here, the loss of life expectancy in nonsmokers is estimated at nine-tenths of a day, to four days in smokers.

A. (cont'd.) McDonald, et al, did not give their data on mesothelioma, so that risk is not included. But they had eleven mesotheliomas and about fifty excess lung cancers, so you can..that will give you some idea of how including those would affect these estimates.

Q. Does that mean it might be another half day?

A. I think something on that order of magnitude.

Q. So that if you were to add the data to include mesothelioma risks, you might be talking about something less than a day and a half for nonsmokers, and something slightly less than three days for smokers?

A. I think it would probably be the same for smokers and nonsmokers because I wouldn't assume a smoking effect, but it would be...I don't think it would materially affect these results. I'm sure they would be less than four days...still less than four days for smokers, and less than two days, certainly, or a day and a half for nonsmokers.

But I can't say for sure.

MR. HARDY: Mr. Chairman, there are two other areas that I think Dr. Crump is going to want to address. One is some review we have done of some of the animal inhalation data with respect to risk assessment, and also he wants to talk a little about some of the mesothelioma prediction issues that Mr. Peto mentioned last week. I think the grand total would probably take about a half hour. I wondered whether you would want to take a break now and we'll come back and do that half hour?

DR. DUPRE: I think it might be appropriate to take a break.

Could I ask the counsel this, during the break period, see if you can get some idea on the amount of time that you will need for your questions, as I have to bear in mind our options, if Dr. Crump is willing to let us have these options,

DR. DUPRE: (cont'd.) would be to perhaps either try to sit until about seven o'clock and wrap this up for the day, or alternatively, perhaps break about five-thirty to return at some...

MR. HARDY: We'll pool our ideas and hope we come up with a good compromise.

DR. DUPRE : Let us rise until quarter to five.

THE INQUIRY RECESSED

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THE INQUIRY RESUMED

DR. DUPRE: Will you proceed, counsel, please?

MR. HARDY: Fine.

(few words missing due to technical problems)

MR. HARDY: Q. ...asbestos textile factories, and maybe you can just briefly tell us what you were able to learn from those studies?

THE WITNESS: A. I did apply the same general procedures to the Rochdale data and the Dement data, which are both textile operations.

Q. We are looking at table fourteen now, which is in the middle of the addenda. It was, unfortunately, out of order.

A. I didn't go into as much detail with these estimates as I did with the McDonald estimates. I essentially accepted everything the authors said at face value, and just expressed their estimates in different forms.

For example, Peto very crudely estimated relative risk for lung cancer, I think between two and three, from certain crude average exposures, and I just simply took the midrange of those numbers he gave and translated those into additional risk and loss of life expectancy. There was no data on smokers. I just...I didn't fit any smoking data, or anything like that.

A. (cont'd.) For Dement, he did have some table of cumulative exposure versus relative risk. I did actually fit a line to that data and used that fitted line as a basis for estimating these numbers.

Q. With the Dement data, I gather, you accepted the exposure information the way he presented it in his preliminary report?

A. Right. Right. And there is one feature about the Dement study which is different from some of the other studies in that he moves people from different exposure categories as the exposure increases, which other studies didn't do. Whatever their total exposure is, they go into that category and all their person-years of experience fall into that same category.

He moves people from one category, from a low-exposure category to a higher-exposure category as their exposure increases over time, and I took that into account in making these estimates. If one does not do that, but simply does the same thing he does with the other kinds of studies, it would lead to somewhat overestimates, higher estimates at least, of these numbers for risks and loss of life expectancy.

We see here that the same relative pattern between smokers and nonsmokers holds as held for the McDonald study, but the absolute numbers are much larger. Where we had three hours for the McDonald study - loss of life expectancy - the comparable number for Peto's study is three days, three and a half days.

Even though on the surface these studies look very similar, they are both primarily chrysotile and they are both textile operations, the risks of the Dement study are much higher than they are from the Peto study.

DR. UFFEN: When you say you took it into account that he would move people from one category to another, how did you do that? Did you put them back?

THE WITNESS: No. All I did was very simply, as I estimated my exposures in my future population, the risk to a future population, I did the same thing with their exposures. I made a compensation there, when I estimated what their exposures were. That's all I did. It wasn't very, terribly difficult to do, actually.

MR. HARDY: Q. You talked about the nonsmoker results for the Peto and Dement studies, and maybe we should mention the smoking results.

THE WITNESS: A. Yes. Well, again, the risk to smokers is...turned out to be about twelve times as great, and that would...it's really a function of the basic relative risk to smokers and nonsmokers irrespective of asbestos exposure, that just exists anyway and which gives you that figure.

But further comparisons...

Q. Maybe just to put those loss of life expectancy numbers into context then, I want to look at table fifteen.

A. Let's see. Okay. For smokers, we have loss of life expectancy ranging from forty-one to two hundred and ninety days. Compare that with some estimates of loss of life expectancy for other causes, and well, one thing you could observe is that even using the Dement study the loss of life expectancy looks like it's going to be not a very sizeable fraction of the loss already incurred from the smoking without the asbestos exposure, although certainly a much larger fraction than it was using the McDonald data.

Still, these numbers are still the same orders of magnitude as the numbers - loss of life expectancy from occupational accidents.

Q. Okay.

A. They fall into the same range.

Q. I believe, Dr. Crump, you have taken a look at some of the animal data and looked at it from the perspective of risk assessment, which is a subject, unlike one we have spent most of the time up to this point on, in that it's an area, I think, where it would be somewhat virgin territory for this Commission.

Maybe you could talk about what value the animal studies have for risk assessment.

A. I think they can help us answer some kinds of questions dealing with relative differences in the different types of fibers. It's a very difficult problem, it's hard to get a handle on just using the occupational data.

They can answer the question of what dimension of fibers are biologically active, and help us reach a conclusion there.

There are a couple of studies that I wanted to bring to your attention, present you some results from, and the first of these is not an asbestos study at all. It's a study on the implantation of glass fibers into the pleurae of rats, by Stanton.

Stanton et al had previously implanted different fibers, different types of asbestos, glass fibers and other types of fibers into the pleurae, and determined that the solid, long-lasting fibers tend to induce pleural cancers regardless of the type of material the fiber is made from.

This study that this slide is taken from is a study on their part attempting to determine the effects of fibers of different dimensions upon carcinogenicity. They implanted...I forget how many...but there were a fair number of fibers, samples generated of different dimensions and different distributions of lengths and widths. They implanted these fibers into the pleurae of rats and waited to see if cancers developed.

This slide is sort of a summary of this work and

A. (cont'd.) shows the correlation between fiber length and fiber diameter, and tumor production.

Q. This is table twenty-two?

A. Table twenty-two.

Their basic conclusion is, as you can see from this table, that first of all short fibers between zero and eight microns, regardless of length, don't correlate very well at all with tumor production.

Q. You mean regardless of diameter?

A. Yes. I said length.

Short fibers, regardless of diameter, don't appear to correlate very much at all with tumor production. Large fibers, regardless...thick fibers, regardless of length, don't correlate well at all with production of these tumors, but you get a very nice correlation between long, thin fibers and the induction of tumors...which suggests that at least proximal carcinogenicity, the biological activity is determined by the proportion of long, thin fibers. That appears to be the more biologically active dimensions.

This does not speak to the problem of getting the fibers there and their transport in the body, but this at least deals with, once the fibers get there, with proximal carcinogenicity.

The other study I want to show you is an inhalation study. There have been a number of inhalation studies starting back in the 1950's. The first one to show a relationship with the inhalation of fibers and induction of tumors being (inaudible).

This slide is the next one...

Q. I think...no, it's twenty.

A. I really want the one before that, nineteen.

Q. Right.

A. Since the later 1960's, there have been several

A. (cont'd.) studies which showed a relationship between inhalation of fibers and, asbestos fibers and production of tumors.

Incidentally, the only positive response that had been found had been in a rat, although a number of other species have been investigated.

I want to just talk about the most recent of these studies, as far as I know, which is the Davis et al, 1978, study, in which they exposed rats for a year to various concentratons of the three asbestos fiber types, and did observe the animals for their remaining lifetime to see what tumors were induced.

Their study was designed to investigate the noted effect of mass fiber versus fiber counts, so they applied... they gave one group of animals ten milligrams per cubic meter of amosite, and they gave two other groups equal concentrations of crocidolite and chrysotile. They exposed two other groups to chrysotile and crocidolite, at concentrations designed to give the same number of fibers greater than five microns, and they came close to succeeding here. You see that they get three hundred and ninety fibers per milliliter of chrysotile, four hundred and thirty crocidolite, and five hundred and fifty amosite, and in the experimental design they were trying to get those numbers the same. They came relatively close to it.

They wanted to see what the tumor production pattern would look like in this situation.

Here is just a summary of the results, table twenty: No tumors in the control animals; the exposures to crocidolite - they have three tumors total, at the high dose of crodicolite they only had one tumor; with the amosite exposure they had two tumors. However, they had significantly more for chrysotile exposure. They had nine tumors at the low exposure and fifteen tumors in the high exposure, which, just on the surface,

A. (cont'd.) would indicate that in this particular situation chrysotile was more dangerous than either amosite or crocidolite.

What I want to do is to show how this difference can be explained from fiber dimensions, so I want to go back to the previous slide, table nineteen, and call your attention to the bottom row.

Not only do they count fibers greater than five microns, they also counted fibers greater than twenty microns, and you see at the chrysotile exposures you had significantly more fibers, long fibers, than you had in the other kind of exposures - even though the fibers greater than five microns, there were comparable concentratons of those.

I'm going to present a chart that sort of looks at the data from that angle.

Before I do, there is one other little thing I want to point out: They also kill some animals along the way and measured the content of asbestos in the lungs, by weight. They found, by the way, there was far more crocidolite and amosite in the lungs, by weight, than there was chrysotile. This has been verified by other investigators, that chrysotile doesn't seem to reside in the lungs as long...or at least you don't get the same concentrations in the lungs at equal exposures as you do in the other two fibers.

But the thing that I want to point out here, that I want to give, is that at the low chrysotile exposure of two, and the high chrysotile exposure of ten, that's a difference of five. But if you look at what was actually in the lungs at the end of the exposure, instead of having five times as much, there was only about a little over two times as much, which indicates that there may have been a saturation effect and the actual effective dose to the lungs was less at the high exposure

A. (cont'd.) than what might be indicated just by knowing how much they were exposed to. I want to take that into account in trying to understand the data.

Okay, now this figure three, I have taken these three measures of exposure which were available in the study - mass, milligrams per cubic liter, fibers greater than five microns and fibers greater than twenty microns, and plotted those against tumor production, and I've also given the error bars of these tumor production rates.

If you look at tumor production versus mass...by the way...you can tell what corresponds to crocidolite exposure, you've got CR there, amosite exposure you have AM.

If you look at the data, you just get a scatter plot. There seems to be no relationship between dose and tumor production. If you account for the possible saturation of the highest chrysotile dose by moving that over, that doesn't seem to help the correlation at all. In fact it gives you what looks like an inverse relationship to an exposure and tumor production.

If instead of using mass you use fibers greater than five microns, which is what is currently being measured in human populations, the situation is not improved very much. You still get nearly an inverse relationship between exposure and tumor production.

However, if you use longer fibers still, fibers greater than twenty microns, the situation begins to make sense and you do begin to get a reasonable dose-response relationship between fibers, dose and tumor production.

In fact, if you do account for the saturation, the highest dose, and move this dose over here to the highest crocidolite and chrysotile exposure, you do get data that will describe a simple linear relationship. This seems to be in keeping with the finding by Stanton that the long, thin fibers seem to

A. (cont'd.) be the ones which are biologically active, and it appears to me that this study adds strength to that argument - not only in terms of its proximal carcinogenicity, but total carcinogenic process of inhalation, deposition and removal of fibers.

DR. UFFEN: I'm a little slow at reading things. The scale on the left - tumor response probability - is that a logarithmic scale...?

THE WITNESS: Yes, that is a logarithmic scale.

DR. UFFEN: So we've got a logarithmic scale across the bottom too?

THE WITNESS: Right.

DR. UFFEN: So the linear relationship is between the logarithms of the probability and the number of fibers. Have I got that right?

THE WITNESS: Yes. But in fact it's actually a linear relationship between the actual numbers themselves, not just the logarithms, because this line has in fact sloped one. The slope is one, and that's the linear relationship betweeen the actual numbers.

I spent actually quite a bit of time trying to decide the best way to show this data, and I finally decided a log...

DR. UFFEN: It's just a little hard to see there, but you can see it on the printed...

THE WITNESS: Yes. Both, actually the log actually is, but this linear relationship is in fact purely linear, not because the slope is in fact exactly one. The slope of the log scale is one, which means an actual linear relationship between the values.

DR. UFFEN: Okay. It's a good job it's one. If it was three or four we would have...

THE WITNESS: A quadratic, or a fourth degree fit. But it is one.

One thing that this suggests is that it would be good to have data in human populations on the distribution of fiber dimensions, rather than simply counting fibers greater than five microns. We had that...if we had such data we might be able to make sense of the seemingly greater risk from fibers of certain types, or certain types of operations, than others.

It's possible that it could be explained in terms of different fiber dimensions. Unfortunately, I don't know of any data available in human exposure that would allow us to really answer that question.

The animal data indicate that that might be the case.

MR. HARDY: Q. I believe you've also looked at the animal data in terms of estimating some risks to illness?

THE WITNESS: A. I have. I'll just show that to you quickly.

Table twenty-three fits the data in this study that I'm talking about to a mathematical dose-response model, and actually this is the same model as the EPA uses for calculating water quality criterias, a method that I developed for them for doing so. Those are based upon animal data.

The method is essentially equivalent to drawing a straight line through the data. It's linear and it's roughly just a fancy way of drawing a straight line.

I hate to say that, but it's true.

Well, when I used the dose unit of fibers greater than five microns, I computed...this is actually estimates to carcinogenic potency. I computed those differently for amosite, crocidolite and chrysotile because it seemed like if the...well, you saw the data, there was no relationship until I put them all

A. (cont'd.) together. As you might expect, I got the largest potency from chrysotile. You had no tumors from chrysotile at comparable exposure levels of fibers greater than five microns.

For fibers greater than twenty microns, I felt it was reasonable to combine them all and I got those potency estimates there. Unfortunately, there are no data on human exposures measured in fibers greater than twenty microns that I can apply that to.

Q. Table twenty-four?

A. Table twenty-four.

I went beyond this step that I have here to do the exercise of converting these risks to risk in humans under a two fiber per milliliter standard, and to do that exercise you've got to use some way of converting animal risks to human risks, and that is a very uncertain process.

I used three methods. I give the results here from these three methods.

First, I assumed that a given concentration, just in fibers per milliliter, is the same carcinogenic potential in rats and humans, given that exposure covers roughly about the same proportion of an animal's lifespan to a human's lifespan.

The next estimate was based upon a given dose in fibers per kilogram body weight per day as the same potential in rats and humans.

The third method is a surface area conversion procedure which says that a given fiber count in fibers per square meter of surface area per day - the slash is missing there - is the same potential in rats and humans.

These methods have been used at various times for doing this sort of thing, I might add, with not a great deal of justification. There have been some very limited studies where you have data in animals and rats - not with fibers though, to see

A. (cont'd.) which of these methods give the closest correlation between estimates based on animal data and estimates based upon human data, and based upon limited data this conversion here seems to give the best correlations.

Q. That's the middle conversion?

A. Yes.

Q. Roman Numeral II?

A. Yes. Roman Numeral II. Although the data from which that statement is made is in fact quite weak, very limited. But it's the best that we have.

I'm not sure what to say about this, except that these numbers span about the same ranges as the numbers I presented earlier based upon the human data. They are not...the lowest estimate of risk is not too far from the lowest estimate of all those that I presented, and the highest estimate of risk is very close to the estimates of, I believe, in smokers in the Rochdale data.

DR. MUSTARD: Can I ask you one question about your estimate on that? In your table nineteen, you showed us that chrysotile had more fibers greater than twenty micrometers in length than the crocidolite exposure.

THE WITNESS: Yes.

DR. MUSTARD: So that that's in that calculation, isn't it?

THE WITNESS: No, it's not.

DR. MUSTARD: Isn't it? Have you corrected for that?

THE WITNESS: No. This is just based solely upon the concentrations of fibers greater than five microns.

DR. MUSTARD: No, but what I'm saying is that if you assume that the long, thin fibers are the most hazardous, and put that into the calculation...if I understand what you've done, correctly...then I can interpret this risk is not just a risk for amosite and crocidolite and chrysotile....you can also interpret

DR. MUSTARD: (cont'd.) this as a risk from where you've got the greatest proportion of long, thin fibers. The data you gave in table nineteen is that the greatest portion of long, thin fibers was in the chrysotile exposure.

THE WITNESS: Yes.

DR. MUSTARD: Therefore, rather than looking at the names...

THE WITNESS: The type of..

DR. MUSTARD: ..I could put type of fiber down and I would be getting maybe an estimate of what that risk is. If I assume that both forms of asbestos are equally potent, that it's the fiber shape and size that's the determinant.

THE WITNESS: Yes. That's true.

I guess the reason I didn't present the estimates in that way is that I didn't have any estimates of human exposure expressed...

DR. MUSTARD: I realize that.

DR. DUPRE: Let me see if I follow this. Would I understand from the interchange you just had with Dr. Mustard that you can just as easily, instead of using asbestos-type labels, perhaps have used fiber dimensions?

THE WITNESS: I think that's roughly what we are saying.

DR. MUSTARD: That's right. If I take his table nineteen, the mean number in terms of fiber..

THE WITNESS: If I accept...

DR. MUSTARD: ...dimensions, what's quoted here, rather than just type, greater than twenty micrometers in amosite was six, crocidolite was seventeen, I believe, and chrysotile was seventy-two.

MR. HARDY: Q. One final subject I think I would like to have you address, Dr. Crump, is when we were last together

Q. (cont'd.) here in Toronto, we heard a good deal about predicting mesothelioma risks, from Mr. Peto. I know you have taken a look at the models for predicting incidence rates of mesothelioma that he presented, and I would just like to get your views on that model.

THE WITNESS: A. We could use a slide here as a framework for discussion.

Q. Shall we get a number to that slide? That was one in the addenda that we added. I think if we label it twenty-five, that's the number that we haven't used anywhere else.

A. This slide shows a couple of things. First of all, it has two columns which give the mesothelioma mortality rates broken down by ages since first exposure, in the Selikoff et al study of insulation workers.

This column gives the latest figures that appear in the Peto et al, 1981 paper. This column gives the same type of measurements, just not quite as current, based upon this followup taken from an earlier paper by Selikoff.

This one number down in the lower V here is actually taken from even an earlier study. The comparable number was listed in Selikoff et al, 1979.

These data, these mortality rates are roughly comparable. There is very little difference in them materially, no material difference.

Q. You are saying there is not much difference between the rates Selikoff found when he had several more years of followup?

A. The updated study, in the 1979 study, the rates are roughly comparable and the reason I'm using the...actually the reason I even bring up the older rates is primarily because I had made some calculations based upon and I didn't want to redo them.

A. (cont'd.) The rate past fifty years of age is slightly lower in the older data than it is in the newer data. This might be due to the fact that Peto ignored all deaths past eighty years of age in computing this number and I don't think that was done in computing that number. I might be mistaken, but that could account for some of that.

As I'm sure you know, Peto fit a model to this data which assumes that the risk increases as T to the three point five power, and gave some justification for doing that, and he only fit the data above the dotted line and did not use the data below the dotted line. As a matter of fact, those data do not fit his model at data point. The risk actually shows a decrease after fifty years past first exposure and does not continue upward.

That decrease could possibly be due to misdiagnosis in old age, although I think a point could be made, an argument could be made that may be a true down turn. For one thing, Peto has already removed all the deaths past age eighty and is not considering them, so a lot of the deaths at extreme old age have already been removed.

Another reason is that Selikoff went to great lengths to ascertain cause of death here, and I think did a good job of determining the true cause of death.

So I think it's conceivable that that down turn could be real and not a result of misdiagnosis.

Q. I gather that what you are saying then is that there may be a time after first exposure when the mortality rate doesn't continue going up, but in fact starts going back down?

A. Yes. In fact, that may happen here past fifty years of age. That down turn, I think, could be a real down turn.

It seems to me that it's somewhat unlikely that given you have an exposure, no matter what happens after that the risk keeps continuing on going up at this very rapid rate, even

A. (cont'd.) after exposure stopped.

There are no data that I know of that give us any information on what happens more than thirty years past termination of exposure for mesothelioma, and I think it's conceivable that the risk could turn around and go down. They certainly do for lung cancer fifteen years or more after exposure is stopped. They do turn around and go back the other way.

So it's possible that could happen for mesothelioma as well.

Okay, Peto fit the model ignoring the exposures past fifty years and came up with these incidence rates here...or I guess I came up with those...using Peto's three point five power.

Q. At this point you are talking about, just for the record, the column under...

A. This column.

Q. ...Fit of Models to Selikoff in the first column, the T to the three point five power?

A. Yes. And I can't recall right now if I just copied numbers he came up with, or if I actually did the fitting myself. I think I copied his someplace.

He did this fitting by ignoring this down turn here, and you can see that it doesn't fit data too well at all down here. It continues up, whereas the data exhibit a down turn.

I don't really have any quarrels with that, that that could be wrong necessarily. My only point would be that that is one plausible model and that there are other plausible models which should also be investigated that might be equally as plausible, fit the data equally as well, but give one different results, and we should investigate the magnitude of the differences one would get using such models.

DR. UFFEN: Do you recall why Peto didn't use those data?

THE WITNESS: Didn't use?

DR. UFFEN: The ones below the dotted line.

THE WITNESS: He said that this was probably due to under-reporting in old age, and was not a true measure of what the true incidence was...as I recall.

DR. UFFEN: Have you any idea how many cases this represents, the down turn, or expressed relative to the total number?

THE WITNESS: I think his total...I'm not sure, really...I think his total number of cases is fairly small.

He is also deleting person years at risk after age eighty, at the same time, so he is assuming that people are lost to view after age eighty. That's basically what he is doing.

DR. UFFEN: What I'm trying to get at is, did he leave out something significant or was it one or two cases?

THE WITNESS: Well, I think there's a fair number of cases here. Even after leaving out those cases, you see the incidence at fifty years past first exposure, there is still a significant shortfall there, as would be predicted by his model. That is, I think, highly significant, particularly if you are going to be trying to predict the risks, say from exposure of school children, where they have a long time for those risks to accumulate.

Well, one thing I did to explore this issue was to use another model in which incidence accumulates as T minus thirteen years squared, and fit that model to these data. There is a biological argument that would lead to a model such as this. For example, if the induction of mesothelioma is a three-stage process and once you have actually induced the mesothelioma there is roughly a thirteen year waiting period until the expression of the cancer, or death from a cancer, then one would actually get the model which I have here.

THE WITNESS: (cont'd.) When you fit that model to the data, it fits equally as well as the Peto model, and actually fits slightly better. But both of them fit well enough that you couldn't say that there is any difference in terms of fits.

So here are two models which fit the data equally well, and you can give some biological argument for each of the models. The question is, what difference does it make when you estimate risk.

Well, if you estimate risks up to fifty years past first exposure, it doesn't make any difference. Because they both fit the data, you could use the actual data themselves and get the same thing with all three methods.

The only time it makes a difference is when you extrapolate at old age.

To give some idea of the magnitude of the effect, I have...

MR. HARDY: If I may make this table twenty-six, it's the very last table in the addenda.

THE WITNESS: So I could give you some idea of the magnitude of the effect, I have calculated the probability of dying of mesothelioma following exposure as a child in schools at one fiber per milliliter. As a matter of fact, I have used exactly the same assumptions that Peto used in an earlier analysis of health risks from exposure to schools, so the only difference in these numbers...I think what's crucial here...the only difference in these numbers is the way that you accumulate the time. Everything else is treated exactly the same, and you can see the difference it makes.

The total risk up to age eighty is reduced by about fifty percent...not that much, but point zero three eight, point zero two five...if you used the T minus thirteen squared model versus the three point five.

THE WITNESS: If you use the actual incidence rates found be Selikoff, for all ages past fifty years exposure just apply that one value he had there, you get numbers which are even lower still, which are about one-third as great as those you get using the T to the three point five factor.

I don't think there is any basis for determining which of these techniques is more valid than any other at this point. I think they all have about the same basis as far as curve fitting and biological rationale.

I would also like to point out that all the data that we have observations on is data above this dotted line, so everything down below here is speculation based upon fitting the models to the data - extrapolating beyond the point of observation.

Just to give you some idea of how the extrapolation goes, to come forward extrapolating, the largest incidence rate... observed incidence rate at any age here is ten point eight, observed in the Selikoff data. But to calculate these risk estimates...if I can thoroughly confuse you here...if we just look at what is down at the bottom...to calculate these numbers here in this column from the Peto method, the incidence rates went up to twenty-nine, which are about three times the observed incidence. That's all based upon projections beyond the range of the data.

MR. HARDY: I think I'll let Mr. Laskin ask some question now, except I think it looks like the chairman would like to.

DR. DUPRE: Just before I recognize Mr. Laskin, could you just clarify one thing for me? The actual incidence rates column found be Selikoff et al, these are actual incidence rates among whom?

THE WITNESS: The incidence rates come from this paper here, from this column here.

DR. DUPRE: Okay.

THE WITNESS: All I did was the past fifty years since first exposure, apply this single number from thereon out.

DR. DUPRE: So this is incidence rates among the insulation workers.

I assume from what Mr. Hardy has just said that you wish to be first in the batting order?

MR. LASKIN: For as long as my voice holds out, Mr. Chairman.

DR. DUPRE: As for your colleagues, what is our time horizon at this point?

MR. LASKIN: Well, I think probably amongst us we might go to seven o'clock, assuming the witness...the witness may want a break or the Commissioners may want a break.

DR. DUPRE: I think, Dr. Crump, we are very much in your hands. If you could bear with us until seven or shortly after seven, perhaps there will be a way of giving you the evening, or what's left of it, off.

THE WITNESS: Okay, let's give it a shot and see how we do.

DR. DUPRE: Thank you.

Proceed, counsel.

MR. LASKIN: I'll do my best to be brief.

CROSS-EXAMINATION BY MR. LASKIN

Q. Dr. Crump, can we come back to your comments about doing quantitative risk assessments and the criteria that you listed, and I would just like to ask you a few questions about the McDonald paper and how that, the study, and how that fits in with your analysis.

Did I take your evidence correctly to say that in terms of your second criteria, quality of exposure data, that you

Q. (cnt'd.) would give the McDonald study high marks, even in terms of doing a risk assessment in fiber measurements, not particle measurements?

A. Relatively speaking, I would give it high marks. Relative to other data which are available in other studies.

Q. Is it fair to say when we are looking at that issue of exposure data and when we've got measurements in particles, that generally speaking we've got to be concerned with two elements, number one, how accurate the particle measurements were in the first place, and number two, how accurate or how well correlated the conversions from particles to fibers are?

A. Yes.

Q. Is that fair?

A. Sure.

Q. Dealing with the first element - that is the particle measurements - were you aware, in terms of McDonald's own study, that for the period 1904 to 1949, which as I understand it comprised about two-thirds of the period of study of his analysis, there were virtually no measurements at all?

A. Yes.

Q. So that looking at the whole spectrum we've got about a forty-five year period in which, out of a seventy-one year analysis period, in which we virtually have no, even particle measurements?

A. I think there were some measurements prior to 1950, but they weren't nearly as extensive as those...they were very limited.

DR. DUPRE: I think the reporter perhaps didn't hear your answer.

THE WITNESS: A. As I recall, there were a few measurements prior to 1950, but they were very limited measurements.

MR. LASKIN: Q. As I understand it, the estimates

Q. (cont'd.) were essentially made on the estimates that Mr. LaChance and Dr. Gibbs did between 1949 and 1966?

A. I think that's essentially correct.

Q. Do you take account of that factor when you make the judgement that the McDonald study is still relatively good in terms of quality of exposure data?

A. I think so. They did have some detailed...they had detailed work histories which they used. Yes, they had to estimate previous exposures, and this is a shortcoming. But, you know, still, relatively speaking, I would give it high marks.

Q. Would you at least agree that that's not a shortcoming of the Rochdale study, at least insofar as the data from 1951 onwards is concerned?

A. In what respect?

Q. In the sense that there were actual measurements?

A. From 1951...

Q. Yes.

A. ...onward?

Q. Yes.

A. There were measurements in the McDonald study from 1951 onward.

Q. Right. But Dr. McDonald's study, would you agree, his 1980 analysis, does the whole period? There's no breakdown as between the period before 1951 and the period after 1951?

A. Oh, you are saying the analysis of the response since 1951, using the Rochdale data would be preferable to the analysis...stronger than the analysis made by McDonald of the total data?

Q. Well, I don't know. I'm really just asking you because it seems to me that the one advantage that the Rochdale data had, at least in terms of actual measurements, is that it

Q. (cont'd.) had those measurements for a period in which a mortality was done.

A. Yes.

Q. And McDonald didn't have that advantage?

A. That is an advantage. However, as far as the study itself is concerned, the raw data, it's not necessarily an advantage because the data do exist for the McDonald study to do the same type of analysis. I wasn't ranking, you know, the actual... ranking the data base more so than I was the analysis of the data.

Q. You say the data exist to do the same thing with McDonald?

A. Yes.

Q. All right. In the sense, you mean, that you could start from 1951 and work forward?

A. Yeah.

Q. Right. Then let's turn to the second item, and that is the conversions from particles to fibers, and I noted that the first study you talked about in that sense was a paper by Dagbert.

A. Yes.

Q. Which is...you'll have to help us, because that's a paper that we are not entirely familiar with as yet...but do I take it that that paper concerned some side-by-side particle and fiber measurements?

A. That's correct.

Q. But do I also take it that none of those side-by-side measurements were done during the period which Mr. LaChance and Dr. Gibbs did their actual measurements for the McDonald study? In other words, they were done later in time?

A. I believe that's the case, right. I'm not sure exactly when those measurements were made. I presume they were made in the early seventies.

Q. That's my understanding.

So I would take it that at least one of the assumptions that would have to be built-in to those measurements would be the assumption that the relative ratios between particles on the one hand and fibers on the other would be the same for the period 1904 through to 1966, as in 1971?

A. You did have to extrapolate those, you know, relatively dustiness versus fiber counts, backwards, and there is simply no data back there to determine if that assumption is correct.

Q. Right. Right.

In terms of Dagbert's actual calculations, I have some trouble in determining what significance one should attach to the correlation coefficients that you listed on the board, and can you give us some sense as to the reliability of a correlation coefficient that is point three four, as it was in mine twenty-nine, or point five seven?

A. Well, it's easier to explain the significance rather than the actual meaning of the number. It's not just the size of the number, but the significance one attaches to it, and all of those numbers were highly significant which means that it's unlikely that there is no relationship between fiber counts and dust measurements.

Q. What would the correlation coefficient have to be before you could say there was no relationship between fiber counts and dust measurements?

A. It depends upon the number of observations available. It's not a function just of the size of the number, but the number of observations available.

Q. All right. Given Dagbert's number of observations, can you give us any help?

A. Not off the top of my head, no, I can't.

Q. Okay. Did you look at the similar attempt by LaChance and Gibbs themselves to work out a correlation coefficient between their side-by-side...between their own measurements?

A. I looked at their 1974 paper, which lists those, and the discussion. I don't recall a formal analysis of those side-by-side measurements.

Q. Can I show you a paragraph from the Simpson Report, which I think really summarizes what Gibbs and LaChance conclusion was in respect to that matter, and perhaps ask for your comment on it?

It's in Mr. Steele's appendix analysis at page eighty-five, paragraph seven.

A. Would you like me to read it?

Q. No, why don't you just take a moment to read it to yourself and maybe you can give us some comment on what the significance or otherwise of their conclusion was.

DR. DUPRE: What paragraph are you referring to?

MR. LASKIN: Paragraph seven.

THE WITNESS: Page eighty-five.

M. CASGRAIN: Would you mind, Mr. Chairman, if it was actually read? I don't have the reference. If it was read I could understand the question and answer better. It couldn't be that long, surely.

MR. LASKIN: Sure.

DR. DUPRE: Do you wish to read it, counsel?

MR. LASKIN: Perhaps the witness would like to read it. He's got it in front of him. I don't have it in front of me.

THE WITNESS: I would be happy to read it.

MR. LASKIN: His voice is better than mine.

THE WITNESS: I'm not sure about that, but I'll be happy to try.

"Over the period 1971 to 1972, surveys were

THE WITNESS: (cont'd.) "conducted by Gibbs and LaChance at up to nine selected sites in each of five mines and mills of the Quebec chrysotile asbestos mining and milling industry. A total of eighty-seven pairs of membrane filter and midget impinger samples were collected.

The linear correlation coefficient for fifty-six samples with more than one fiber per field was point three two, and after a logarithmic transformation of both variables, the correlation was increased to point four five.

For thirty-one samples with less than one fiber per field, the correlation was almost zero - parenthetically, minus zero point zero three - end of parentheses, and the correlation of logarithmically-transformed data was zero point two five.

If membrane and impinger counts were considered by work site, it was clear that the ratio of the two differed from mine to mine and varied with the stage of production within the same mine or mill.

It was concluded that correlation was poor and no single conversion factor was justified."

Now, you want me to comment on that?

Q. Please, if you would.

A. In relationship to what I've said?

Q. Yes, sir.

A. Well, first of all the data that I have reported on that Dagbert analyzed is six hundred and thirty measurements, rather than eighty-seven. It's a far larger set of data.

The correlations in this larger data set are higher than the ones are here, and I'm sure they are much more significant

A. (cont'd.) than...since they are based on a larger sample.

They found essentially the same effect that I was reporting, that when you have low exposures the correlations go down, if you have higher exposures the correlations go up, and that there seemed to be a difference in effect in different mines, and also effects in different mining operations. This is the same effect found by Dagbert when he analyzed...I didn't show you that...when he analyzed different production operations, he found different ratios than he found for the...well, different operations had different conversion factors.

Q. When you did your own correlations were you using a logarithmic calculation or a...

A. I actually didn't do any analysis. I'm just reporting the analysis that Dagbert did.

Q. Are those his own correlations?

A. Yes.

He did logarithmically transform the data.

Q. Can you briefly, in laymen's terms, tell us what the significance of doing that is, since you seem to get different results?

A. Well, when you do a correlation analysis the theoretical justification for some of the confidence limits and significance tests that you run says that you need a normal bell-shaped curve of observations, and it just so happens that instead of studying the actual observations themselves, if you study their logarithms in this particular set of data you get a more bell-shaped curve than you do with the actual observations.

Q. Can you tell us whether these correlations...

DR. MUSTARD: Excuse me, counsel, can I ask a question?

MR. LASKIN: Sure.

DR. MUSTARD: Is what you mean then, if you look at the distribution of the actual data, that you find that it does not have a normal distribution, that it has a log normal distribution?

THE WITNESS: It's more adequately described by log normal than normal.

DR. MUSTARD: That's true for both kinds of measurements?

THE WITNESS: I believe so. Yes.

MR. LASKIN: Q. Can you tell us whether these correlation coefficients relate to all of the jobs within a particular mine, or are they done...are they isolated out job by job?

I don't know if I'm making myself clear, but...

THE WITNESS: A. He did things in two different ways. First, he looked at the correlations within different mines over all jobs, and then he did the correlations in different work areas over all mines.

Q. Was there a better correlation if you did it by job as opposed to doing it by mine?

A. Well, I don't think you can really answer that. The correlations are all significantly positive in all the mines. That was not true with all work practices. The ones that had very low, on average, particle count measurements, there was no significant correlation.

Q. Okay. Can you take these correlation coefficients that you've got and translate them into conversion ratios? Can you...let's...that's perhaps not a very good way of putting it, but what I'm really asking you is, can you, on the basis of whatever these correlation coefficients tell you, develop some range of conversion ratios?

A. Yes. One can do things like this: Given an average exposure count in terms of particles, one can set limits

A. (cont'd.) on what the average exposures in terms of fiber counts would be.

Q. Have you done that, or has Dagbert done that in respect of his data?

A. He did..

Q. Or can you tell us?

A. He did one thing in which he took single particle count and constructed a confidence limit for single fiber count.

To my thinking, that's not particularly the relevant thing to do. What one is interested in, rather than that, is given an average exposure level in terms of particle counts, what are the confidence limits on the predicted average exposure levels in terms of fiber counts. He did not do that.

There is...the variation between individual paired measurements is not as important, in my opinion, as when you look at averages, because the average exposures are the ones which are things of interest.

Q. Is there, in your judgement, sufficient correlation between the average exposures to convert particles to fibers with some sense of confidence?

A. That you are really doing something? Yes.

Q. That's your judgement?

A. Yes.

Q. As a statistician?

A. Yes.

Q. I take it you are aware that Dr. McDonald himself, in some of his writings, has indicated that he doesn't feel that it would be justifiable?

A. Well, I don't know if he thinks it would be justifiable or not. He has done it in recent papers.

Q. For what purpose?

A. For what purpose? In his most recent study... maybe not most recent, but a recent study...he took all of his exposures measured in terms of particles, on an individual basis, and converted each of those to exposures on a fiber count basis, using the data in the Dagbert study and other data as well, and then he reanalyzed the data using these new exposure measures to see if he got any significant differences. It turns out he did not.

Q. I'm just looking at a sentence, a statement he made in his New York Academy paper, which was written in 1979 and included his latest study, where he said: "Conversion from particle to fiber counts would be desirable, but it is not, in our opinion, justifiable if precision and certainty are required".

As a statistician, would you agree with that?

A. I'm going to have to...before I say I agree, get you to repeat the statement again, please.

Q. Sure.

"Conversion from particle to fiber counts would be desirable, but is not, in our opinion, justifiable if precision and certainty are required."

A. That's such a vague statement I can't really say if I agree with it or disagree with it. You certainly can predict with certainty fiber counts from impinger counts. I certainly think there's very useful information gained by doing so, so I guess in that sense I would disagree with his statement.

Q. Can we go to your calculation which you have still got up on the board?

A. Sure.

Q. Which I take it again is based on Dr. McDonald's data?

A. Yes.

Q. Let me see if I understand all of the assumptions that are built in to that calculation. I take it assumption number one is that a person will work only twenty-five years?

A. No, that's not an assumption.

Q. All right. Will accumulate asbestos fibers or particles of dust for the purpose of calculation, for twenty-five years?

A. No, I don't think that's an assumption either.

Q. No?

A. In the particular cohort that these estimates were made from, they had exposures past twenty-five years which are not included, but the exposures were still there which contributed to health effects. So this calculation would be would give the same result of, you know, the relative levels of exposures were comparable past age forty-five as prior to age forty-five. That would be one way in which you can get the same results.

The other way would be if the exposures past age forty-five did not contribute very much to overall health risks.

Q. But the forty-five minus twenty years that you've got there, I take it, signifies that you are accumulating fibers for twenty-five years?

A. If a person...well, I had to use the data which was actually used by McDonald, and the particular study that I used, the dose measure he used was total exposure - cumulative exposure to age forty-five. In order to make my estimates, I had to ask this question: Given occupational exposure throughout life, what is the cumulative exposure to age forty-five. That was the appropriate measure to plug into that formula.

Q. Because that's the only calculation that he

Q. (cont'd.) did when he analyzed smoking and nonsmoking data?

A. That particular data that I used, that's the dust measure he used. Right.

I have actually applied the same technique to... although there wasn't smoking data available...to the data on which he had exposures...there is a cohort he has there in which he separates out exposures which are twenty years in length or greater, and doesn't just stop at age forty-five and have redone the analysis...even though smoking data are not available...and came up with roughly the same results.

Q. All right.

The second thing I take it you did was, is that you made an assumption that if there is a standard of two fibers per cubic centimeter or per milliliter, in actual fact persons will be exposed only to one fiber per cubic centimeter or milliliter?

A. That's right.

Q. All right.

The third thing I take it you did was that you made some adjustment in terms of personal as opposed to static sampling?

A. Yes.

Q. And applied a factor of two?

A. Right.

Q. Why did you do that?

A. Because these measurements that were made, fiber count measurements made in the McDonald et al cohort, were based upon static samplers, and there is evidence that when you use personal samplers you get something different. It's very uncertain, you know, what...how the difference goes, but the reason I used two is because that was the figure recommended

A. (cont'd.) in the Simpson Report and I haven't seen any better data available, so I've just decided to use that value.

Q. That was the figure used out of Rochdale?

A. It's the figure given by the Steele's report in the Simpson Report.

Q. Based upon static measurements using the thermal precipitator as opposed to personal membrane filter measurements?

A. I don't know. I do know that the Simpson Report has a footnote to those risk estimates they give that if you want to convert from static sampling to personal sampling, you have to use a factor of two.

Q. But I'm just wondering why it was done, because nowhere in any of McDonald's writings that I can find does he suggest that there should be that adjustment that should be made?

A. I don't think he was asking the same questions that I've been asking. He wasn't going the step that I have taken in estimating risk to some cohort, which would be exposed to something based upon a two fiber standard which is enforced using personal samplers.

So I don't think it was necessary for him to take that step.

Q. But isn't another way of looking at it that you are really calculating excess risk or additional risk based on a standard of point five fibers per cubic centimeter?

A. I don't think that's the way to look at it.

Q. Well, if you eliminate the two assumptions that you've made - that is that actual exposure will be to one fiber, and that you should make an adjustment for personal sampling - that's the effect of it, isn't it?

A. I don't think it's an assumption, strictly

A. (cont'd.) speaking, that a standard of two fibers per milliliter will result in a one fiber exposure. I think that there's data to back up that it may be in fact less than that, the actual exposure.

I will agree with you that what I have there is risk from not a standard, but exposure to high fiber per milliliter measured with a personal sampler, assuming again, making an assumption that the factor of two, going from personal to static, is a valid step.

Q. You have made your caculations, therefore, on a lifetime exposure of twelve and a half fibers-per-cubic-centimeter years?

A. That's not the appropriate interpretation of that.

One had to use...the fact that I used twenty-five years does not mean that that risk is from exposure to twenty-five years. The question is, given lifetime exposure what's the exposure accumulated to age forty-five, and that's the dose measure used in the McDonald study.

Q. Four point zero million particles-per-cubic-foot years, using Dr. McDonald's conversion ratio of three point one four, translates out to about twelve and a half fibers-per-cubic-centimeter years. Isn't that right?

A. Yes.

Q. And that's the basis for the calculation you made?

A. What is the basis for the calculation I made?

Q. That...

A. That formula there...

Q. That cumulative exposure?

A. That explanation I've given is the basis for it.

Q. But that's the cumulative exposure that you

Q. (cont'd.) are working from when you make the calculations?

A. What's that?

Q. Four point zero million particles-per-cubic-foot years, or twelve and a half fibers-per-cubic-centimeter years?

A. Accumulated to age forty-five.

Q. Yes.

A. Yes. But that also does not...it also accounts for exposures past that age.

Q. You've explained that.

Why do you place the availability of smoking data so high on your list of criteria?

A. Because the relative risks of smokers versus nonsmokers, of lung cancer, is so large that if smoking rates in the exposed group are off somewhat from those in the general population, it can make a sizeable difference in the risk estimates...in the...yes, in the risk estimates. In the relative risks, also.

Q. I'm trying to get some sense of when smoking data, or the absence of it, will matter. If the smoking habits of the general population from which you calculate your expecteds are roughly the same as the smoking habits of your exposed population, will smoking data still be important?

A. The smoking habits in the general population? I think you have to worry about how those are partitioned out into the different exposure categories. I would be worried about that also.

Q. All right. If we make yet another assumption that they are generally distributed about the same way, then do we have to worry as much about smoking habits?

A. I would like to be able to, you know, check the assumption, the multiplicative assumption, which can be done without

A. (cont'd.) the data, but beyond that, given what you say, it would not...not having the data would not affect the estimates greatly.

Q. How well do you rate McDonald's study in terms of its availability of smoking data?

A. I rate it high.

Q. Relative to other studies or in absolute terms?

A. I think in absolute terms.

Q. What did you understand his smoking data to be?

A. It's based on a questionnaire which was administered to the workers or their survivors, for those who had passed away, and it went back only to...it only went back to 1950. They did not try to ascertain the smoking habits of people that died prior to 1950.

Q. Which, as I understand, was nearly twenty percent of the total number of deaths?

A. Most of the people that died, died of nonasbestos-related diseases...of the ones that died prior to 1950.

Q. So, I take it, you don't place any great significance on the absence of smoking data for that number of persons?

A. I believe I would be correct in this, that the analysis of the smoking data that I showed accumulates from the time smoking data were made available.

Q. How do you rate the Dement study in terms of the criteria that you gave us?

A. Overall I give it a fairly high rating, just on what I observe in reading the paper.

Q. Is there any...looking at your six criteria, are there any of the criteria where you feel the Dement study falls down or doesn't deserve high marks?

A. Not in any significant area. I mean, it's, you know, it's exposure primarily to chrysotile, there's exposure data

A. (cont'd.) available, they are not individual smoking measurements but they do have some overall smoking rates in the population which indicates they aren't very different from those in the general population.

I think he had a predominance of short exposures as opposed to other studies, but overall I wouldn't give it a low rating based on those criteria.

Q. Have you had an opportunity to look at Dr. Weill's study?

A. Yes.

Q. Could you give us your judgement on how it fares according to your criteria?

A. Okay. He has exposure to chrysotile and crocidolite. They are mixed exposures...although he can separate out a subgroup which had exposure only to chrysotile. He had individual smoking, individual exposure data available. I'm not familiar with the details of how that data arose.

Smoking data are not available, as I recall. He had a fair number of short-term exposures, and he had some long-term exposures, too.

I would give it probably an intermediate grade.

Q. I won't ask you where that stands and find out whether you are a tough marker or an easy marker.

What judgement do you make, or what significance do you place on the fact that Dr. Weill had what I understand to be a missing trace rate of around twenty-five percent?

A. I don't recall the trace rate was quite that... the missing rate was quite that high. I don't recall exactly what it was.

I can't think of a way that...a reason that would bias his results. I would certainly prefer to have a higher trace rate.

A. (cont'd.) I understand that he is undertaking a new analysis and they trace some of those untraced people.

Q. Yes.

In your judgement did he make a fair assumption about those missing persons to assume that they were all alive?

A. I think so.

Q. Why do you say that?

A. Well, if they are alive, they haven't contributed to the observed numbers of deaths from asbestos-related diseases. Whereas in fact they might have, so it should result in, if anything, an underestimate...or an overestimate, of the relative risk.

Q. Can I just bring you back to your calculation which is on the board there, but applied to table fourteen where you did some preliminary analysis of your application to Peto's 1980 study and Dement's 1980 study, and could you...perhaps you can't do this, and certainly tell us...I mean without a lot of calculation...but could you tell us how you got to the figures that you got for Dr. Peto?

I only ask it because he went through a very lengthy analysis using his own data to tell us something about what he said was the excess risk, using his own figures, and I'm not sure whether they are ad idem with yours or not.

A. Okay. Let's see.

We might just take a look at Peto's paper.

Q. Sure, by all means.

Maybe I could ask you one threshold question and we might find out whether we are on the same wavelength.

As I understand it, Peto started his calculations from an assumption of one data point, which was...or he had a relative risk of five based upon eight observed deaths as opposed to one point six two expected, and he was talking about persons

Q. (cont'd.) twenty-plus years from first exposure. I guess I should ask you, do you start from the same point?

A. I started from this point right here: Two hundred to three hundred fiber per milliliters per year and a relative risk between two and three, so I simply chose a midrange of those values - two hundred and fifty for exposure and a risk ratio of two point five.

MR. HARDY: Perhaps for the record we should identify the document that we are discussing.

MR. LASKIN: The witness is referring to exhibit thirty-seven, tab seven, page 833.

MR. LASKIN: Q. Then can you tell us briefly what you did?

THE WITNESS: A. Okay. I assumed that two hundred and fifty fibers per milliliter years resulted in a risk ratio of... a relative risk of two point five, which is the midpoint of the range that Peto gives, and rather than trusting to my memory perhaps I had better look this up.

I've got that, which says that the relative risk, and we use a linear model for relative risk, is one plus...this is one point five divided by two-fifty, times dose, or one plus point zero zero six D for fiber per milliliter years, so...in other words, if you plug in the two hundred and fifty here, you get the relative risk of two point five and it's a linear model.

Okay, this is based upon a fixed sampler, and a graticule grid method of counting fibers.

Okay, then exposure from age twenty to age sixty-five under a two fiber per milliliter standard would result in an estimated cumulative exposure of sixty-five times twenty years times point five fibers per milliliter, which is twenty-two point five fibers-per-milliliter years.

This was the dose which I used in that equation.

Q. What's the end relative risk figure? It's one plus point zero zero six times twenty-two point five?

A. Yes.

Q. Is that then translated into either of the figures that are shown on table fourteen?

A. Yes.

Q. Which one?

A. It translates into all four of the figures shown on table fourteen.

You apply that to smoking, incidence rates for smokers, and you get the...

Q. In the general population in Great Britain?

A. Just specifically on smokers. You know, you have incidence rates estimated for smokers smoking eighteen cigarettes per day, and then you apply that to those incidence rates and come up with those figures.

Q. Then you...do I take it those are incidence rates in Great Britain for the general population?

A. It's taken from a study of British doctors.

Q. Doll's study that you referred to before?

A. Yeah.

Q. What does the figure one over one hundred additional risk mean? If you translate that into words, what does that mean?

A. Okay. You look at the lifetime probability of dying, of a smoker dying of lung cancer, without exposure to asbestos. Then you look at the lifetime risk of a smoker who is also exposed in this context I have here on the board, to asbestos... his lifetime risk of dying of lung cancer, and take the difference. That's where that figure comes from.

Q. A one one-hundredth greater risk for smokers?

A. Yes.

Q. Without going through the calculation, can you

Q. (cont'd.) just tell us what your starting point was when you made the calculation for Dr. Dement?

A. Yes. Dr. Dement has a table in which he has relative risks versus exposure, and different exposure categories. So to estimate the potency parameter, I fit a linear model to that data and the parameter that gave the best fit is the one that I used for the calculations on Dement.

Q. If I showed you his paper could you tell us the data that you were working from, to do it?

A. Sure.

Q. It's exhibit four in our proceedings.

A. Table seven, the data for lung cancer in table seven.

Q. Just one other question about your calculation with respect to Peto, I was just trying to get some sense as to whether you and he started from the same place and if my assumption is correct that he started from his one data point, that is eight observed over one point six two expected, which, as I understood, gave a relative risk of five at a lifetime exposure of a hundred fibers per milliliter years. It would appear you didn't start at the same points.

A. Okay. I would have to look and see, but I started from those values that he gives in his last page or so.

Q. Right. Which appear to relate back to table number three in this paper. I don't want to get too technical about it, but I'm just trying to get some sense as to whether you were working with the same figures or not.

A. Okay. Would you like for me to take a look at that?

Q. Well, if you can do it quickly. I don't want to waste your time.

A. I have to trace back and see, actually. You're asking did I start with the eight observed

A. (cont'd.) and one point six two expected?

Q. Right.

A. No, not exactly. Peto says here...perhaps I could read what he says: He says, "The observed relative risks for lung cancer twenty or more years after first exposure in post-1950 employees was four point nine. This is significantly higher than that observed in men entering between 1933 and 1950, but as a majority of pre-1950 employees in this study were still employed in 1951, it seems likely this apparently-marked increase in risk is largely due to chance.

The eventual relative risk for lung cancer among men with estimated cumulative exposures of about two hundred to three hundred fiber-per-milliliter years is therefore between two and three".

Those latter figures are the ones that I used.

Q. Do you have any judgement on the quality of the risk assessment that was actually done in the Simpson Report, taken as a whole?

A. No, I think, you know, some of the things I thought they did were a little bit crude and could be done in a more refined way. As far as saying, you know, it was a bad assessment or a good assessment, I guess I don't have a blanket statement to make on that.

Q. Can you be a little more specific than when you say it was done crudely?

A. Well, they took the slopes that you get the potency estimates from, from various studies, in which the exposure measures weren't exactly comparable, and sort of use them all interchangeably as if they were comparable. Then when they accounted for smoking they used essentially a figure of, as they

A. (cont'd.) say, well, about one-tenth...I think the risk of lung cancer in smokers is about one-tenth, so we'll use that figure. They didn't use the age structure of incidence rates, so in those respects I thought maybe it was fairly crude.

Q. What about their choice of studies for inclusion?

A. They used the Rochdale study, and they used Enterline's study and they used the McDonald study. I think those studies pretty much satisfy the essential things which I think are most essential. There is some measure of exposures, and they do have some defined types of fibers that they are looking at.

Q. Had you to do a risk assessment yourself in 1981, can you tell us what studies you would place on your list and what studies you think sufficiently meet your criteria to do a quantitative risk assessment?

A. It depends upon what population and what exposures I was trying to assess risk in. I might have to use some studies that don't measure up to my criteria because of that.

Q. If you were dealing with a jurisdiction that had no mining whatsoever and had to deal with setting a standard for asbestos exposure solely in the manufacturing and perhaps end-user situations, what studies would you use?

A. I would try to pick studies in which the people were exposed in similar operations to similar fiber types. I think that would be an important consideration.

Q. Does your own...are you suggesting by that that we should be looking at particular standards for particular phases of the asbestos industry?

A. I wasn't necessarily making that leap. I was just speaking strictly about trying to estimate risk and saying that, very basically, fiber type and operation seems to make a difference so one should try to match up a study with the type of operation for which you are trying to estimate risks.

Q. Of all the studies that we have been talking about today, let me just ask you, are there any that you think are not sufficiently good enough that you would exclude from any risk assessment?

A. That I would totally ignore any consideration?

Q. Yes.

A. No, I wouldn't say never use this study for any risk assessment activities - any of them.

Q. Are there any whose weight you discount?

A. Well, that's again a hard question to answer until you look at the particular application. I think, you know, generally, studies which don't have exposure measures, estimates you get from them are very uncertain.

Q. Do I take from that that if we find that any of the studies we have been talking about that do have exposure measures, you are prepared to at least take into account in some respect?

A. I certainly wouldn't rule any of them out at this point. In fact, I wouldn't rule out, you know, just not knowing what situation we are dealing with, I wouldn't rule out any study whether they had exposure measurements or not.

Q. Are there any studies we haven't mentioned that you are aware of that you think are good studies and ought to be given some consideration?

A. The recent study by Newhouse and Berry in the...

Q. The Ferroda plant?

A. I don't know the name of the plant - the friction materials plant - I think should be given some consideration.

Q. Any others?

A. Well, maybe some I'm not familiar with as I should be. I'm not that familiar with the recent studies done in the plant locally, and I wouldn't really have a judgement on that

A. (cont'd.) right now.

Q. Can I just finally ask you one or two questions about your article, which is at tab one of your compendium?

I suppose the question I want to ask you relates to some evidence that Dr. Kotin gave when he testified before us, and I won't paraphrase his article. What I really wanted to do was ask you about another article which seems to address the same subject, and which Dr. Kotin referred to. That is Dr. Cornfield's article.

First I better ask you, are you familiar with that article?

A. Do you have the exact title of the article?

Q. Yes. I had it a minute ago. It's called, Carcinogenic Risk Assessment, and it's found in the November, 1977, issue of Science.

A. Yes, I'm familiar with that.

Q. As I understand it, and this may be my simple layman's understanding of this article which may be completely inaccurate, he seems to be making out a case for, as he calls it, a kind of hockey stick dose-response relationship based on a theory that there is a deactivization process that might occur at low doses. I just wonder whether you have any comment or judgement on his approach in that article.

A. This article has been apparently misunderstood from what the author intended. He first shows a simplified version which shows an actual threshold, and then later he has said that he wasn't really proposing a threshold model, but he was really talking more about the hockey stick type of situation.

Other investigators have, you know, at least theoretically, come up with the same sort of hockey stick type of a curve when you have a very slow increase, and then once you saturate the protective mechanism it shoots up at a very rapid

A. (cont'd.) rate. I think that's certainly a possible mechanism.

I don't know of any hard data that support that particular theory.

Q. The one comment he seems to make about your study in his own article is, he says that your argument depends on an additive assumption which he says is not supported by experimental data, I take it?

A. Well...

Q. Do you have any comment on that?

MR. HARDY: Would Dr. Crump like to read it? It may be a while since he has looked at what Dr. Cornfield said about him.

THE WITNESS: I think I...maybe I should look at it.

MR. LASKIN: Sure. It's at page 695.

THE WITNESS: I had this article memorized at one time. As a matter of fact, one of my comments on this article was published subsequently in Science.

Yes, this is quite a controversy, you know, of whether the dose-response curve is linear or not. I think Cornfield is really starting at the wrong point here. He is saying that, "The additive assumption is one that lacks experimental support", and that's certainly true, but the important thing here is that one does not need perfect linearity, just an absence of perfect independence, to get the results that we've come up with.

Q. In terms of your own model, do I understand it correctly that you say that asbestos as a carcinogen would fit into the analysis that you presented in tab one?

A. Yes. I would say that, you know, that article would pertain to asbestos as well as other fibers.

Q. Would it pertain to asbestos not only in

Q. (cont'd.) relation to lung cancer, but also in relation to mesothelioma?

A. Well, I think I need to be more specific in order that I not be misunderstood. What the article says is that when you have background incidence that it really had to be cancer of any kind...where you have background levels. Then this argument leads one to the conclusion that you would expect the dose-response curve to be approximately linear at low doses.

The argument depends upon the existence of a background effect, and when I say linear I don't mean just, you know, draw a straight line through all the data. I mean at very low doses the rate of change is approximately linear, but it could still be curvilinear at higher doses.

The argument for linearity, based upon that, I think would pertain more particularly to lung cancer in smokers than it would to mesothelioma or certainly I don't think it's very appropriate for asbestosis, or even lung cancer in nonsmokers, as it does to lung cancer in smokers.

Q. Does your article address in any way the issue as to whether asbestos is an initiator or a promoter?

A. No, the article really doesn't mention asbestos, as I recall.

Q. Sorry. Let me take it more generally. Whether a particular carcinogen is an initiator or a promoter?

A. It's been so long since that article was written, I would have to look at it to see if we discussed that or not. We do say at one point that this argument will...I think I read it a few moments ago...now I've forgotten...I think we do discuss, you know, initiation versus promotion. I'm not sure exactly at what point we discussed that.

Would you like me to look for it?

Q. Does it matter to your analysis...let me ask

Q. (cont'd.) you this...does it matter to your analysis whether a particular carcinogen is one or the other?

A. To the analysis estimates that I made...?

Q. The analysis that you find in tab one?

A. Oh. Yes, I think that should be taken into account and you can argue...I think you would have to be more specific to determine the effect of a promoter versus an initiator.

I think the argument there for linearity is not particularly based upon something being an initiator as opposed to a promoter.

Q. That's really what I was getting at.

Does your argument, if you become more specific and apply it to asbestos, does your argument on linearity depend upon whether you characterize asbestos as an initiator or a promoter?

A. Well, not per se. If it, you know, promoted in some way which doesn't occur without the asbestos exposure, then it might not, you know, apply directly. If it doesn't, then there is some mechanism which...it's not the mechanism through which cancers which are already there are occurring, then it might make a difference.

Q. Has your own research into asbestos health effects enabled you to make any assessment as to whether it is an initator or a promoter?

A. Not really.

Q. When you were talking about linearity, I noted a statement down that you said that most data in the asbestos field are, I think you said, are supported by the linear model.

A. They are adequately described by a linear model.

Q. Are there any that are not?

A. I'm guessing that the asbestos data I presented

A. (cont'd.) on Seidman probably cannot be described by the linear model.

I haven't actually checked it, you know, done the test to see. But I don't know for sure of any data that are not well described by the linear model.

Q. Why do you say that the risk is not apt to be much greater than predicted by a linear relationship, but may in fact be less?

A. Because I don't know of any plausible models of carcinogenesis which predict a superlinear type effect, and I don't know of any...that's a general statement...scientific opinion, I don't know of anyone really proposing such a model.

Q. Which, I take it, would be a large S at the beginning, or something to that effect?

A. Pardon?

Q. Drawing it on an axis, I take it a model for which...will enable you to say that a linear relationship is a not a conservative estimate would have to have a large sigmoid-type curve?

A. Well....it would have to have an inordinate amount of increase at low doses.

MR. LASKIN: Yes, something like that.

Q. You say there is nothing that you know of that biologically supports that in any plausible way?

A. That's correct.

Q. Is there anything that biologically supports in a plausible way a curvilinear-type curve?

A. Yes. You mean...when you say curvilinear, you mean like this?

Q. Yes.

A. Yes, there are a lot of reasonable mechanisms that would support that kind of relationship.

Q. Just one final question about your animal data calculation. You may have explained it and I may have missed it, but when you did the calculation going from animal data to human data, was the measurement of fibers that you used only those fibers greater than five or twenty microns in length, in any particular case?

A. Those greater than five microns. That's what I used to compute that last slide that I put up there, that had the estimates of human risks and three different methods of converting risk from animals to humans.

Q. So that am I then correct that your conversion from animal to human, at simpler doses, would not take into account all of the fibers less than five microns in length, say for example, that aren't measured at a particular fiber measure but which, in the ordinary workplace, might well be part of the exposure?

A. Well, they take it into account in the sense that if the proportions of those in the animal population and the human population are the same, you would get the same results, the risk estimates would still be valid.

It also takes into account in a sense that if those fibers are in fact biologically inactive, then you would get the same results.

Q. How plausible is the first assumption, I mean in the animal experiment world what percentage of the fibers that are injected or inhaled are in fact less than five microns in length? Is there any evidence on that?

A. In this particular animal study, I don't recall if there is evidence in the paper or not with respect to that.

Q. Can you help us, by the way, on where this paper comes from, because again I think it's a paper that we are

Q. (cont'd.) not entirely familiar with?

A. The Davis paper? I'll give you the reference.

Q. Could you?

A. Okay. Davis, J.M.G., S.T. Beckett, R.E. Bolton, P. Collings and A.P. Middleton, 1978 - Mass and Number of Fibers in the Patheogenesis of Asbestos-Related Lung Disease in Rats - British Journal of Cancer, 1937, page 673 to 688.

MR. LASKIN: Okay.

Thanks very much, Dr. Crump. My voice has run out just before yours.

THE WITNESS: Just barely.

DR. DUPRE: Mr. McNamee?

CROSS-EXAMINATION BY MR. McNAMEE

Q. Yes, you referred to the Dement study. I understand that his control population was the U.S. population at large rather than the control group in the county in which the plant was located, is that correct?

A. Yes, I think that's true.

Q. I think there has been some criticism levelled that in fact the lung cancer rate in that county, along with, Dr. Enterline said, even the heart disease rate was very high in that particular area and maybe it would have been more appropriate to have as a control group the selection from the county in which the plant was located. Do you have any criticism of that point?

A. It's really hard to say. There's some advantages to using the local population, but on the other hand the local population may have been affected by the very mill that he was studying. I think I would have liked to have seen the calculation done both ways to see what difference it makes. If it doesn't make much difference, then we wouldn't have to worry about that very much.

Q. I think it was also pointed out that in fact this county was the center of a very large ship building operation in the second world war and that there may have been a heavy exposure of asbestos, crocidolite asbestos, to some of the very people who may have later on worked at this same plant?

A. That may be true. I wasn't aware that that was the case.

Q. I don't pretend to understand the study in depth myself, but it didn't appear, the Dement study didn't appear to have the occupational history of the workers prior to entering the plant, and a number of them may in fact have worked in the ship building industry. Were you aware of that?

A. As a matter of fact, I was not.

Q. Mr. Dement indicates that one of the virtues of the study is that primarily chrysotile, if not almost entirely chrysotile asbestos, had been used in this plant, and if in fact some of these people had been exposed or a number had been exposed to crocidolite in the shipbuilding industry, wouldn't that serve to confound some of the statistics?

A. Oh, very definitely.

Q. Just...I tried to tangle with some of the mathematics in Mr. Dement's study and found that I was not quite up to it. What is your overall criticism? Are the mathematics sound? You, obviously, are quite proficient in mathematics. Were you impressed with the mathematics models that Dr. Dement was using...

A. Insofar as they are presented in his paper, from what is presented there I have no real criticism of the way that he did that analysis.

Q. Just for a point of clarification, more personally than anything, when you are talking about loss of life expectancy in days is this taken...who are the control for the loss of life expectancy? Is that the average male American dying at, say seventy-nine years, or some idealized person?

A. No, what you do is, you take a population with a certain set of incidence rates and from those incidence rates you can calculate their life expectancy...without exposure to asbestos. Then under exposure to asbestos, you can estimate what those...how those incidence rates might be modified with a particular exposure to asbestos.

Using those modified rates, you recompute the life expectancy and then take the difference. So it's supposed to be life expectancy in the presence of asbestos exposure, minus life expectancy in the absence of asbestos exposure, then take the negative of that since I started with the wrong one first.

Q. In the same way, it's like some of the control population...you are not taking some idea human that isn't suffering from any disabilities?

A. No.

Q. He is already suffering from some portion of these life-shortening disabilities?

A. Yes. He assumes he has those and it's based upon the incidence rates in the general population.

Q. One other...you have talked about the animal implantation studies of Stanton, and do I understand that at least with glass fibers it is possible to create in a laboratory these finely-sized samples of fibers, like one particular size, or different sizes? It is quite possible, technically, now to create different-sized fibers with precision, is that correct?

A. I'm not really, you know, particularly versed on the exact state of that art. In the Stanton study they had each...there was a distribution of fiber dimensions in all of the ones that he was looking at. I don't think you would say any one was a pure, you know, only contained one fiber dimension.

Q. You wouldn't be aware of whether it's possible, say in a laboratory, to say we'll create a sample composed only of fibers longer than five microns and more than three-to-one

Q. (cont'd.) aspect ratio?

A. I'm really not familiar with the extent to which that's feasible.

MR. McNAMEE: Thank you, doctor. Those are my questions.

DR. DUPRE: Thank you, Mr. McNamee.

M. Casgrain?

M. CASGRAIN: I have no questions.

DR. DUPRE: No questions?

Dr. Uffen?

DR. UFFEN: I asked mine earlier.

DR. DUPRE: Dr. Mustard?

DR. MUSTARD: Mine have been answered.

DR. DUPRE: I have one question or two questions, Dr. Crump.

If I go to your table two which you had back on the board, do you have that accessible to you at the moment - Distribution of Asbestos Dust Exposure Levels in Different Manufacturing Industries?

THE WITNESS: Yes.

DR. DUPRE: The source was the Health and Safety Executive?

THE WITNESS: Yes.

DR. DUPRE: Is this a specially-prepared table that was made available to you, or is this...?

THE WITNESS: No, it's in the Simpson Report.

DR. DUPRE: Oh, this is right out of the Simpson Report?

THE WITNESS: Yes.

DR. DUPRE: Okay, thank you.

My only other question relates to the following: If I go to the tables in which...I guess I'm looking at table

DR. DUPRE: (cont'd.) twelve, as good an example as any. If I got to that table in which you show loss of life expectancy caused by lifetime exposure over a two fiber per cubic centimeter or milliliter standard, I assume it would be relatively easy to calculate the same thing at a one fiber per milliliter standard?

THE WITNESS: Yes.

DR. DUPRE: Would doing it at one fiber simply result in about halving...

THE WITNESS: Yes.

DR. DUPRE: That's all?

THE WITNESS: Essentially.

DR. DUPRE: It's quite a mechanical thing. It falls right out of those equations that you discussed with Mr. Laskin?

THE WITNESS: Yes.

DR. DUPRE: Fine. Thank you very much.

Any final questions of your witness, counsel?

MR. HARDY: No, I don't think so, Mr. Chairman.

DR. DUPRE: Well, may I, sir, thank you indeed for the time you have spent with us and for the evident preparation you devoted to our benefit. Thank you very much.

I understand, Miss Kahn...well, first of all I should shut up and let you say something, is that correct?

MISS KAHN: We are just wondering whether we should check with Arthur Sampson to see whether the witnesses have safely arrived in Canada.

DR. DUPRE: From my knowledge of his airline, of course, if he is on that flight it does not leave Detroit until approximately 8:35 this evening. It will arrive in Toronto at 9:30.

But of course if he is on another flight...

MISS KAHN: He might be on another flight, apparently, from California.

Shall I check?

MR. SAMPSON: We can probably run upstairs, we can check.

MR. HARDY: I would encourage you to call, just in case they know. I think we can assume since they haven't called that everything is okay, but why not double check.

MISS KAHN: Okay.

DR. DUPRE: In any event, shall we simply take it that we rise until nine a.m. tomorrow morning?

MR. LASKIN: Yes.

DR. DUPRE: Unless Miss Kahn informs us to the contrary upstairs.

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THE INQUIRY ADJOURNED

THE FOREGOING WAS PREPARED
FROM THE TAPED RECORDINGS
OF THE INQUIRY PROCEEDINGS

Edwina Macht

EDWINA MACHT